2012-1031

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NOVO NORDISK INC. AND NOVO NORDISK A/S,

Plaintiffs-Appellants,

v.

PADDOCK LABORATORIES, INC.,

Defendant-Appellee.

Appeal From The United States District Court
For The District of Minnesota
In Case No. 10-CV-2199, Judge Donovan W. Frank

PRINCIPAL BRIEF FOR NOVO NORDISK

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CERTIFICATE OF INTEREST

Counsel for Appellants Novo Nordisk Inc. and Novo Nordisk A/S certifies the following:

1. The full name of every party or amicus represented by me is:

Novo Nordisk Inc. and Novo Nordisk A/S.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Novo Nordisk Inc. is a wholly owned subsidiary of Novo Nordisk US Holdings, Inc. No publicly held company owns 10 percent or more of Novo Nordisk Inc.'s stock. Novo Nordisk US Holdings, Inc. is a wholly owned subsidiary of Novo Nordisk A/S, a public limited liability company. Novo Nordisk A/S is the only publicly held company that owns 10 percent or more of Novo Nordisk US Holdings, Inc.'s stock.

Novo A/S, a private limited liability company, is Novo Nordisk A/S's controlling shareholder. No publicly held company owns 10 percent or more of Novo Nordisk A/S's stock. Novo A/S is a wholly owned subsidiary of the Novo Nordisk Foundation, a Danish self-governing institution. No publicly held company owns 10 percent or more of Novo A/S's stock.

Novo Nordisk Foundation has no parent company, and no publicly held company owns 10 percent or more of its stock.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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STATEMENT OF RELATED CASES

This appeal is a companion case to the appeal pending as *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.*, No. 2011-1223 (Fed. Cir.). Order, Nos. 2011-1223 & 2012-1031 (Fed. Cir. Aug. 15, 2012).

Several other pending cases could potentially be affected by this appeal. *Novo Nordisk Inc. v. Aurobindo Pharma Ltd.*, No. 2012-1388 (Fed. Cir.); *Novo Nordisk Inc. v. Lupin Ltd.*, No. 1:10-cv-03750 (S.D.N.Y.); *Sandoz Inc. v. Novo Nordisk, Inc.*, No. 2:11-cv-13594 (E.D. Mich.); *Novo Nordisk Inc. v. Sandoz Inc.*, No. 3:11-cv-06106 (D.N.J.); *In re Prandin Direct Purchaser Antitrust Litig.*, No. 10-cv-12141 (E.D. Mich.).

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. § 1338(a), and entered final judgment on August 30, 2011. Notice of appeal was timely filed on September 26, 2011. This Court has jurisdiction under 28 U.S.C. §§ 1292(c)(2) & 1295(a).

STATEMENT OF THE ISSUES

The District of Minnesota entered a final judgment of invalidity and unenforceability in this case based solely on the collateral estoppel effect of the final judgment previously entered by the Eastern District of Michigan in *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.* This appeal presents the following questions:

I. Whether the final judgment entered by the District of Minnesota in this case (*Paddock*) should be reviewed by this Court only after the Court reviews the final judgment entered by the Eastern District of Michigan in the previous case (*Caraco*), which the court below afforded collateral estoppel effect.

II. Whether the final judgment entered by the Eastern District of Michigan in *Caraco* is legally erroneous and should be afforded no collateral estoppel effect in *Paddock* because, as explained in the companion appeal:

A. The Michigan court erred in concluding that the patented method is invalid as obvious because a skilled artisan would have expected the results achieved by the inventors; and

B. The Michigan court erred in concluding that the patent is unenforceable for inequitable conduct on the basis of supposed "omissions" from the truthful submissions made by the patentee's agents during prosecution.

STATEMENT OF THE CASE

Claim 4 of U.S. Patent No. 6,677,358 claims a method of using repaglinide in combination with metformin to treat type 2 diabetes. A30. On May 28, 2010, Novo Nordisk Inc. and Novo Nordisk A/S filed a complaint in the United States District Court for the District of Minnesota alleging that Paddock Laboratories, Inc. infringed this claim by filing an ANDA for generic repaglinide. *See* 35 U.S.C. § 271(e)(2)(A); A63. Paddock counterclaimed that the patent is invalid and unenforceable. A114.

On January 19, 2011, in separate infringement litigation between Novo and Caraco Pharmaceutical Laboratories, Inc., the United States District Court for the Eastern District of Michigan entered a final judgment declaring Claim 4 of the '358 patent invalid for obviousness and unenforceable for inequitable conduct. A917-A949. Novo filed a timely appeal from that judgment, which is the subject of the companion case pending in this Court as No. 2011-1223 (*Caraco*).

Paddock then moved in the District of Minnesota for judgment on the pleadings based on the collateral estoppel effect of the Michigan judgment. A962-A997. The Minnesota court granted Paddock's motion in part, holding Claim 4 invalid for obviousness and the '358 patent unenforceable for inequitable conduct. A5-A19. With the parties' consent, the Minnesota court subsequently dismissed all remaining claims and counterclaims and entered final judgment. A1-A2.

STATEMENT OF FACTS

This appeal is one of several pending before this Court involving a patented method of treating type 2 diabetes using a combination of two drugs: repaglinide and metformin. A20-A30. The background of the inventive method and the allowance of the '358 patent by the United States Patent and Trademark Office is set forth in Novo's principal brief filed concurrently in companion appeal No. 2011-1223 (*Caraco*), which Novo incorporates by reference herein.

I. The Hatch-Waxman Act Framework

The Hatch-Waxman Act governs certain aspects of the competition between pharmaceutical innovators and their generic counterparts. Enacted in 1984 as an amendment to both the Federal Food, Drug, and Cosmetic Act and the Patent Act, the Hatch-Waxman Act seeks to balance the competing interests of innovators, like Novo, in protecting the fruits of their research and development, and generic manufacturers, like Paddock, seeking to market their own versions of proprietary drugs at the close of a patent term. *See Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1370-71 (Fed. Cir. 2002).

An innovator may not sell a new therapeutic drug in interstate commerce without approval by the Food and Drug Administration ("FDA"). 21 U.S.C. § 355(a). To obtain that approval, the innovator must file with FDA a New Drug Application ("NDA") containing detailed information about the drug's safety and

efficacy (*id.* § 355(b)(1)) and proposed method of use (21 C.F.R. § 314.53(b)-(c)). The NDA applicant must also identify "the patent number and the expiration date" of any method of use patent "with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1)(G). FDA lists this patent information in a publication officially known as the *Approved Drug Products with Therapeutic Equivalence Evaluations* and more commonly known as the "Orange Book," which serves as a reference to generics looking to identify potentially relevant intellectual property. *See Organon Inc. v. Teva Pharm., Inc.*, 244 F. Supp. 2d 370, 374 n.6 (D.N.J. 2002). The current version of the Orange Book is available on the FDA website. *See* FDA, Orange Book, http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

Generic manufacturers seeking to market a copy of an innovator's proprietary drug can file with FDA an Abbreviated New Drug Application ("ANDA"). 21 U.S.C. § 355(j)(1). The ANDA seeks to rely on the innovator's safety and efficacy data by showing that the generic drug "has the same active ingredients as, and is biologically equivalent to, the brand-name drug." *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1676 (2012) (citing 21 U.S.C. § 355(j)(2)(A)(ii)(I), (iv)). Because FDA cannot approve a generic drug that would infringe an innovator's patent, a generic company must include with its

ANDA a statement or certification "that its proposed generic drug will not infringe the brand's patents." *Id.*

As relevant here, the ANDA filer may make what is known as a Paragraph IV certification. 21 U.S.C. § 355(j)(2)(A)(vii)(IV); *TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 72-73 (D.D.C. 2003), *aff'd sub nom. Purepac Pharm. Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004). In a Paragraph IV certification, the applicant certifies that the innovator's listed patent "is invalid or will not be infringed" by the manufacture, use, or sale of the generic drug that is the subject of the ANDA. 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The filing of a Paragraph IV certification indicates the applicant's intent to sell and constitutes an "artificial act of infringement" by the applicant. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990); *see* 35 U.S.C. § 271(e)(2)(A). It is this "artificial act" that serves to "enable the judicial adjudication" of claims for infringement and patent invalidity. *Eli Lilly*, 496 U.S. at 678.

As an incentive for generic manufacturers to challenge branded companies' listed patents and incur the expense of litigation, the Hatch-Waxman Act awards limited marketing exclusivity to the first applicant whose ANDA contains a Paragraph IV certification. 21 U.S.C. § 355(j)(5)(B)(iv)(I). FDA ordinarily will not approve the ANDAs of subsequent generic filers until 180 days after the date of the first applicant's "first commercial marketing." *TorPharm*, 260 F. Supp. 2d at

72-73. Since 2003, however, the Hatch-Waxman Act has provided that a first ANDA applicant can forfeit its marketing exclusivity upon the occurrence of certain events, including appellate affirmance of a district court judgment of invalidity. *See* 21 U.S.C. § 355(j)(5)(D); Pub. L. 108-173, § 1102, 117 Stat. 2066, 2457-60 (2003); *see also infra* at 17-19.

II. The Litigation

In 2005, Caraco Pharmaceutical Laboratories, Ltd. filed with FDA an ANDA to manufacture and sell generic repaglinide, and certified that its sales would not infringe the '358 patent. 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Caraco was the first generic manufacturer to file an ANDA containing a Paragraph IV certification. A2119. Novo timely filed a complaint in the Eastern District of Michigan, where Caraco resides, against Caraco and its parent company, Sun Pharmaceutical Industries, Ltd., for infringement. 21 U.S.C. § 355; 35 U.S.C. § 271(e)(2)(A); *Eli Lilly*, 496 U.S at 678. Caraco counterclaimed for a declaration of invalidity and unenforceability.

Five years later, Paddock submitted its own ANDA seeking FDA approval to manufacture and sell generic repaglinide, and certifying that the '358 patent would not be infringed. A61, A104-A105, A630, A897. Paddock is the fourth ANDA applicant for repaglinide. A2076. Novo timely filed a complaint against Paddock in the District of Minnesota, where Paddock resides, alleging that Pad-

dock had infringed the '358 patent and seeking a declaration that Novo had not violated the antitrust laws. A54-A68.

After unsuccessfully seeking to dismiss Novo's antitrust count and bring a new antitrust action against Novo in Michigan (*see* A478-A492), Paddock filed an amended answer and asserted several counterclaims. A576-A627. As relevant here, Paddock alleged that the '358 patent was invalid for obviousness and unenforceable for patent misuse. A619-A620. Paddock also asserted several antitrust counterclaims under federal and state law. A621-A625.

In January 2011, before any discovery had occurred in the Minnesota action (A18; A897; A903; A973), the Michigan court entered a final judgment declaring the '358 patent both invalid for obviousness and unenforceable for inequitable conduct. A917-A949. Novo filed a timely notice of appeal from the Michigan judgment (A951), and, in the Minnesota action, moved for a stay of the patent litigation pending appeal (A887-A888).

Paddock, in turn, filed a motion for judgment on the pleadings in Minnesota. A962-A963. In particular, Paddock sought a judgment of invalidity "based on the collateral estoppel effect of the Eastern District of Michigan judgment of invalidity of claim 4 of the '358 patent," as well as a judgment of unenforceability "based on the collateral estoppel effect of the Eastern District of Michigan judgment of unenforceability of the '358 patent." A962. Paddock also sought leave to amend its an-

swer to assert defenses of collateral estoppel and unenforceability for inequitable conduct (A974), and moved for summary judgment of non-infringement of the four remaining claims of the '358 patent (A987).

Novo opposed Paddock's motion for judgment on the pleadings. A1540-A1581. It argued, among other things, that collateral estoppel was discretionary (A1549; A1561-A1562), and that the Michigan court's judgment was not entitled to collateral estoppel effect because of conflicting judicial decisions that called into question the Michigan court's subject matter jurisdiction. A1552-A1556; A1564-A1566 (citing *Novo Nordisk Inc. v. Mylan Pharms., Inc.*, 2010 WL 1372437, at *10 (D.N.J. Mar. 31, 2010), and *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 2010 WL 3942727, at *4 (E.D. Mich. Oct. 6, 2010)). Novo also argued that, in light of this Court's then-anticipated clarification of the inequitable conduct doctrine, the Minnesota court should decline to give collateral estoppel effect to the Michigan court's judgment on inequitable conduct. A1556-A1558, A1567-A1568.

On May 25, 2011—after the Minnesota court held a hearing on Paddock's motion for judgment on the pleadings (A2060) but before it rendered its decision—this Court issued its decision in *Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (en banc). Expressly "tighten[ing] the standards for finding both intent and materiality," the en banc Court held that "the accused infringer must prove by clear and convincing evidence that the applicant knew of the

reference, knew that it was material, and made a deliberate decision to withhold it" (*id.* at 1290), and must separately prove that the Patent and Trademark Office "would not have allowed a claim had it been aware of the undisclosed prior art" (*id.* at 1291).

Two days later, in a letter to the Minnesota court, Paddock asserted that *Therasense* "did not change the law in any way that would affect the Michigan Decision on appeal" (A2132), and actually "supports the entry of immediate judgment in Paddock's favor based on collateral estoppel" (A2133). Novo responded with its own letter, pointing out numerous respects in which the Michigan court's judgment of inequitable conduct fell short of the standards announced in *Therasense*. A2134-A2138.

In a June 22, 2011 Memorandum Opinion and Order, the Minnesota court denied Novo's motion for a stay (A18); granted Paddock's motion for judgment on the pleadings based on collateral estoppel (A9-A17); granted Paddock's motion for leave to amend its answer (A8-A9); and denied Paddock's motion for summary judgment on the remaining claims of the '358 patent (A18). Specifically, the Minnesota court concluded that the Michigan court's judgment was valid (A14) and involved "the same issues that are presented in this action" (A12), and that "the Michigan court's conclusions appear to comport with the standards enunciated in *Therasense*" (A17). On August 30, 2011, the Minnesota court entered a final

judgment of invalidity and unenforceability (A1-A2), and dismissed the remaining antitrust claims and counterclaims with the parties' consent (A2614-A2616). Novo filed a timely notice of appeal. A2617-A2620.*

* After this appeal was docketed, Paddock filed a motion for summary affirmance. Appellee's Motion for Summary Affirmance, No. 2012-1031 (Oct. 24, 2011). This Court denied the motion and ordered this appeal stayed pending the Supreme Court's review of an interlocutory issue in Novo's litigation with Caraco. Order 2, No. 2012-1031 (Fed. Cir. Dec. 19, 2011); *see Caraco*, 132 S. Ct. 1670. After that aspect of the Caraco litigation was decided and remanded, this Court issued an order directing that the *Caraco* and *Paddock* appeals be briefed in tandem and argued consecutively. Order, Nos. 2011-1223 & 2012-1031 (Fed. Cir. Aug. 15, 2012).

SUMMARY OF ARGUMENT

This Court should review the judgment in this case (*Paddock*) only after reviewing the judgment in the companion appeal (*Caraco*) because the *Paddock* judgment rests entirely on the collateral estoppel effect of the *Caraco* judgment. And because the *Caraco* judgment is legally erroneous and should be reversed in the companion appeal, the judgment in the *Paddock* case should likewise be reversed.

I. The Hatch-Waxman Act provides incentives and rewards for the first ANDA applicant who challenges a branded company's patents by filing a Paragraph IV certification. Where, as here, the first ANDA filer secures a district court judgment of invalidity and/or unenforceability, the Hatch-Waxman Act does not allow subsequent applicants, like Paddock, to take advantage of the collateral estoppel effect of the first judgment unless and until that judgment has been affirmed by this Court on appeal.

Efficiency concerns also militate in favor of a coordinated, sequential disposition of both appeals. This Court has designated both appeals as "companion cases," and has ordered that they be briefed on the same schedule and argued on the same day to the same panel. The outcome of the *Caraco* appeal will determine the outcome of this appeal. Under the circumstances, it would make no sense to de-

cide this follow-on appeal before deciding the underlying *Caraco* appeal; the *Paddock* "cart" should remain behind the *Caraco* "horse."

II. The Eastern District of Michigan's judgment is not entitled to collateral estoppel effect because it is legally erroneous and should be reversed by this Court, as explained in the companion appeal. Since the Michigan judgment was entered, this Court has clarified the law of both obviousness and inequitable conduct in ways that are irreconcilable with the grounds on which the Michigan court resolved those issues. The intervening decision in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), establishes that the Michigan court misapplied the burdens and standards of proving obviousness. The intervening decision in *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (en banc), establishes that the Michigan court misapplied the burdens and standards of proving inequitable conduct.

Reversal of the Eastern District of Michigan's judgment in *Caraco* requires reversing the District of Minnesota's judgment in *Paddock*.

STANDARDS OF REVIEW

This Court applies the law of the regional circuit when reviewing questions concerning application of collateral estoppel. *Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 435 F.3d 1356, 1359-60 (Fed. Cir. 2006). Under the law of the Eighth Circuit, a district court's application of collateral estoppel is a question of law that the court of appeals reviews *de novo*. *B&B Hardware, Inc. v. Hargis Indus., Inc.*, 569 F.3d 383, 387 (8th Cir. 2009); *Robinette v. Jones*, 476 F.3d 585, 588 (8th Cir. 2007).

Obviousness is a question of law that this Court reviews *de novo*. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty.*, 492 F.3d 1350, 1355 (Fed. Cir. 2007). The Court reviews underlying factual determinations for clear error. *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1346 (Fed. Cir. 2009).

An inequitable conduct ruling is reviewed for abuse of discretion, with the applicable legal standard reviewed *de novo*. *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1374-76 (Fed. Cir. 2007). The district court's factual findings and inferences are reviewed for clear error. *Therasense*, 649 F.3d at 1291.

ARGUMENT

After reviewing the judgment of the Eastern District of Michigan in *Caraco*, the Court should reverse the District of Minnesota's judgment of invalidity and unenforceability in *Paddock*, which was "based on the collateral estoppel effect" of the Michigan court's judgment. A19.

I. The Minnesota Court's Judgment Should Be Reviewed Only After This Court Reviews The Michigan Court's Judgment

On August 15, 2012, this Court issued a joint briefing order in the *Caraco* and *Paddock* appeals. The Court simultaneously lifted stays that it previously had entered in both appeals; designated both appeals as "companion cases"; directed that full briefing in both appeals proceed on identical schedules; and ordered that the *Caraco* appeal (No. 2011-1223) and this appeal (No. 2012-1031) "will be argued consecutively before the same panel." Order 2, Nos. 2011-1223 & 2012-1031 (Fed. Cir. Aug. 15, 2012).

When an initial merits appeal and a subsequent collateral estoppel appeal are designated companion cases, this Court has consistently decided the collateral estoppel appeal concurrently with, or after, the merits appeal. *E.g.*, *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1280, 1292 (Fed. Cir.) (applying collateral estoppel in a follow-on appeal after deciding the companion appeal), *cert. denied*, 132 S. Ct. 2442 (2012); *O2 Micro Int'l Ltd. v. Taiwan Sumida Elecs., Inc.*, 315 F. App'x 266, 267 (Fed. Cir. 2009) (same); *see also*, *e.g.*, *Micron Tech.,*

Inc. v. Rambus Inc., 645 F.3d 1311, 1315 (Fed. Cir. 2011) (en banc) (deciding companion appeal "contemporaneous herewith"), *cert. denied*, 132 S. Ct. 1540 (2012); *Nutrition 21 v. United States*, 930 F.2d 862, 862 n.1 (Fed. Cir. 1991) (deciding companion appeal "concurrently herewith"). Thus, by denying Paddock's motion for summary affirmance and setting the *Paddock* appeal for briefing in parallel with, and argument consecutive to, the *Caraco* appeal, the Court has rejected Paddock's attempt to leapfrog Caraco in the ANDA approval order. That outcome is correct under both the Hatch-Waxman Act and settled principles of judicial efficiency.

A. The Hatch-Waxman Act Does Not Give Superior Rights To "Me Too" Challengers

As this Court's joint briefing order implicitly recognizes, the Hatch-Waxman Act requires that this appeal be decided concurrently with—or after—the *Caraco* appeal. To proceed otherwise would permit a "me too" challenger (like Paddock) to leapfrog the first ANDA litigant and reap the benefits of a final judgment without having to endure either a trial or an appeal. That procedure finds no support in the statutory scheme. *See Caraco*, 132 S. Ct. at 1682-83 (interpreting the Hatch-Waxman counterclaim provision in light of "the statutory scheme").

The Hatch-Waxman Act awards priority to the first generic applicant who submits an ANDA containing a Paragraph IV certification. 21 U.S.C. § 355(j)(5)(B)(iv)(I). FDA ordinarily will not approve the ANDAs of subsequent

generic filers until 180 days after the date of the first applicant's "first commercial marketing." *Dey Pharma, LP v. Sunovion Pharms. Inc.*, 677 F.3d 1158, 1160 (Fed. Cir. 2012) (internal quotation marks omitted). Congress intended this exclusivity to serve as incentive for generic drug manufacturers to file ANDAs early. *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1356 (Fed. Cir. 2008). In this case, Caraco was the first Paragraph IV ANDA applicant; Paddock was the fourth. A906; A992-A993; A2076; A2119. Because Paddock submitted its ANDA more than five years after Caraco (A586-A587; A790), Paddock does not share First Filer status. *See* FDA, Guidance for Industry: 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day (July 2003), *at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072851.pdf (last visited Sept. 20, 2012).

Under certain limited circumstances, a first applicant may forfeit its claim to Hatch-Waxman exclusivity. *See generally* 21 U.S.C. § 355(j)(5)(D). For example, the first applicant may forfeit its marketing exclusivity if it withdraws its ANDA or amends its Paragraph IV certification. *Id.* § 355(j)(5)(D)(i)(II) ("Withdrawal of application"); *id.* § 355(j)(5)(D)(i)(III) ("Amendment of certification"). Likewise, if a first applicant fails to market its generic product within 75 days of a subsequent applicant obtaining tentative FDA approval and a court entering a final judgment of invalidity of unenforceability from which no appeal has been or may be taken,

the first applicant may forfeit its exclusivity. *Id.* § 355(j)(5)(D)(i)(I) ("Failure to market"). The applicant may also forfeit its claim to exclusivity if it fails to obtain tentative approval "within 30 months" after submitting its ANDA. *Id.* § 355(j)(5)(D)(i)(IV) ("Failure to obtain tentative approval").

None of these provisions—including the "failure to market" theory, on which Paddock has proceeded (A2595)—allows a subsequent ANDA applicant like Paddock to use the collateral estoppel effect of a district court judgment of invalidity to force a forfeiture when the underlying judgment is still under review. Rather, the first-filer who secured such a judgment retains its priority until 75 days *after* the appeal is decided. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb). Any other outcome would upend the incentives that Congress put in place to encourage generic manufacturers to be the first applicants to challenge branded companies' listed patents. Indeed, if a subsequent ANDA applicant were allowed to obtain a *pro forma* affirmance based on collateral estoppel while the first applicant continued to litigate a merits appeal, that outcome would create exactly the *opposite* incentive.

At bottom, application of collateral estoppel requires that a court decide "in a principled way whether or not it is just and equitable to allow the plea of estoppel in the case before it." *Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 334 (1971). Here, principles set forth in the Hatch-Waxman Act itself require

that Paddock's appeal be decided concurrently with, or after, the *Caraco* appeal has been resolved by this Court.

B. Principles Of Judicial Efficiency Require A Coordinated Disposition

This appeal and its companion case are being briefed simultaneously and will be decided by the same panel of this Court. Under the circumstances, it would be unwarranted for this Court to decide this appeal before it decides the co-pending *Caraco* appeal. Doing so would place the cart before the horse and could undermine the very basis for applying collateral estoppel.

It is settled that when a "judgment complained of is based directly upon" a judgment the reviewing court has "just reversed," the reviewing court should likewise "reverse the judgment which we know of record has become erroneous, and save the parties the delay and expense of taking ulterior proceedings in the court below to effect the same object." *Butler v. Eaton*, 141 U.S. 240, 243-44 (1891); *accord Maryland ex rel. Levin v. United States*, 381 U.S. 41, 53 & n.38 (declining to consider the preclusive effects of a prior decision because a ruling on the merits made doing so unnecessary), *vacated on other grounds*, 382 U.S. 159 (1965) (per curiam); *Reed v. Allen*, 286 U.S. 191, 198 (1932) (when a collateral estoppel judgment and an appeal of the underlying merits are both pending before the same court, "it rationally may not be doubted" that the court would consider the merits

before affirming the application of collateral estoppel). Similarly, the Sixth Circuit has explained:

> It is well established that "[w]hen a judgment has been subjected to appellate review, the appellate court's disposition of the judgment generally provides the key to its continued force as res judicata and collateral estoppel. A judgment that has been vacated, reversed, or set aside on appeal is thereby deprived of all conclusive effect, both as res judicata and as collateral estoppel."

Erebia v. Chrysler Plastic Prods. Corp., 891 F.2d 1212, 1215 (6th Cir. 1989) (quoting *Jaffree v. Wallace*, 837 F.2d 1461, 1466 (11th Cir. 1988) (per curiam)). *See generally* 18A Charles Alan Wright, Arthur R. Miller, & Edward H. Cooper, *Federal Practice and Procedure* § 4433 (2d ed. 2002) ("In some cases, litigants and the courts have collaborated so ineptly that the second judgment has become conclusive even though it rested solely on a judgment that was later reversed. This result should always be avoided" by, *inter alia*, "delaying further proceedings in the second action pending conclusion of the appeal in the first action" (footnote omitted)).

As Paddock's unsuccessful motion for summary affirmance has shown, there is literally no authority for deciding this appeal *before* disposition of the underlying merits appeal. In both of the cases that Paddock cited in arguing for summary affirmance, this Court ruled on the collateral estoppel appeals only *after* prior panels of this Court had decided the underlying merits appeals. *See Eli Lilly & Co. v. Sicor Pharms., Inc.*, 426 F. App'x 892, 893 (Fed. Cir. 2011) (noting that

the collateral estoppel appeal was "controlled by" the Federal Circuit's prior affirmance of the merits appeal and denial of rehearing); *Abbott Labs. v. Mylan Pharms., Inc.*, 1999 WL 970186, at *1 (Fed. Cir. Oct. 4, 1999) ("The basis for the district court's decision stemmed from a prior suit finding the patent at issue invalid, a finding that this court recently upheld on appeal").

Indeed, in *Eli Lilly* this Court stayed the collateral estoppel appeal so that it could first decide the underlying merits appeal. *Eli Lilly*, 426 F. App'x at 893 ("This court stayed these appeals pending the outcome of the *Sun Pharm.* appeal"); *accord Hanson v. Denckla*, 357 U.S. 235, 238, 243, 254-55 (1958) (coordinating disposition of appeals from Florida and Delaware by holding, first, that Florida court lacked personal jurisdiction over an indispensible party, and second, that Delaware court had no obligation to give full faith and credit to the Florida judgment); *Coyne & Delany Co. v. Selman*, 98 F.3d 1457, 1460, 1472-73 (4th Cir. 1996) (coordinating sequential disposition of first appeal and subsequent res judicata appeal). Thus, this Court should adhere to its unbroken practice and decide this collateral estoppel "companion case" concurrently with, or after, the *Caraco* appeal.

There is no dispute that both appeals present the same substantive issues. Indeed, that is exactly how Paddock obtained its judgment in the district court below. Paddock repeatedly urged the Minnesota court that "the issues sought to be

precluded ... are the same here and in the Michigan Action" (A979), and that "the issues of invalidity and unenforceability of the '358 patent in the Michigan action are the same as in the present case" (A1987). The Minnesota court, accepting Paddock's argument, found that "[t]he issues regarding the invalidity and unenforceability of the '358 Patent are the same issues that are presented in this action." A12.

This Court has ordered that those issues will be briefed on the same schedule, argued on the same day, and decided by the same panel. It is therefore beyond dispute that the outcome of this appeal will depend on this Court's resolution of the issues presented and briefed in the *Caraco* appeal. They should be decided in that order—with the *Paddock* cart remaining behind the *Caraco* horse.

II. The Minnesota Court Erred In Applying Collateral Estoppel

The District of Minnesota also erred in giving collateral estoppel effect to the judgment previously entered by the Eastern District of Michigan. Under the law of the Eighth Circuit, this Court reviews a district court's application of collateral estoppel *de novo*. *B&B Hardware*, 569 F.3d at 387.

In the Eighth Circuit, application of collateral estoppel, also known as issue preclusion, is guided by five factors:

> (1) the party sought to be precluded in the second suit must have been a party, or in privity with a party, to the original lawsuit; (2) the issue sought to be precluded must be the same as the issue involved in the prior action; (3) the issue sought to be precluded must have been actu-

> ally litigated in the prior action; (4) the issue sought to be precluded must have been determined by a valid and final judgment; and (5) the determination in the prior action must have been essential to the prior judgment.

Robinette, 476 F.3d 589 (quoting *Anderson v. Genuine Parts Co.*, 128 F.3d 1267, 1273 (8th Cir. 1997)). As with any equitable doctrine, however, these factors must not be applied rigidly or in isolation. Rather, "no one set of facts, no one collection of words or phrases, will provide an automatic formula for proper rulings on [collateral] estoppel pleas." *Blonder-Tongue*, 402 U.S. at 333-34.

The Supreme Court has repeatedly cautioned that collateral estoppel "must be confined to situations where the matter raised in the second suit is identical in all respects with that decided in the first proceeding *and where the controlling facts and applicable legal rules remain unchanged.*" *Comm'r v. Sunnen*, 333 U.S. 591, 599-600 (1948) (emphasis added); *accord Montana v. United States*, 440 U.S. 147, 157-58 (1979) ("changes in controlling facts or legal principles ... or other special circumstances" may render application of collateral estoppel inappropriate). This limitation on collateral estoppel applies with no less force in patent cases than in other contexts. *See, e.g.*, *Blonder-Tongue*, 402 U.S. at 333 (requiring inquiry into whether first court applied correct test for obviousness); *see also eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006) (principles of equity "apply with equal force to disputes arising under the Patent Act").

The Eighth Circuit has expressly embraced the "Change in Law Exception" to collateral estoppel. *E.g.*, *Ginters v. Frazier*, 614 F.3d 822, 827, 829 (8th Cir. 2010) (reversing district court's application of collateral estoppel in light of a "change in the law"). As a leading treatise explains, "changes in the surrounding legal climate may often defeat preclusion"—including changes that "result from decisional developments." 18 Charles Alan Wright, Arthur R. Miller, & Edward H. Cooper, *Federal Practice and Procedure* § 4425 (2d ed. 2002). That is precisely what has occurred here.

A. Intervening Decisions Make Clear That The Michigan Court Applied The Wrong Law On Obviousness

"The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282; *see also Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2245 (2011) (noting that § 282 "establishes a presumption of patent validity" and "a challenger must overcome that presumption to prevail on an invalidity defense"). As this Court has recently emphasized, that burden always rests on the challenger, and there is "no indication" that "the burden of persuasion should shift to the patentee at some point to prove non-obviousness." *Cyclobenzaprine*, 676 F.3d at 1078.

Here, however, the Michigan court erred in repeatedly and expressly misallocating the burden of proof; and the Minnesota court likewise erred in giving the Michigan court's invalidity judgment collateral estoppel effect. As explained more

fully in Novo's principal brief in the *Caraco* appeal, the Michigan court erroneously required Novo "to prove unexpected results" from the claimed combination in order to "overcome" Caraco's "prima facie case" of obviousness. A942. But Novo had already proven unexpectedness to PTO. A930. As this Court recently emphasized, "shifting the burden of persuasion" on "unexpected results" is legal error. *Cyclobenzaprine*, 676 F.3d at 1075; *see also id.* at 1076 (patentee has no burden to "overcome" the challenger's initial, or *prima facie*, showing of obviousness). And as the Minnesota court failed to inquire whether the Michigan court applied the correct standards for obviousness, its judgment on the pleadings should be reversed. *See* A12 (noting only that invalidity was "actually litigated" in the Michigan action).

Moreover, the Michigan court failed to give the required weight to the Examiner's factual finding that the claimed invention yielded unexpected results. The Supreme Court recently held that a court may set aside factual findings made by a PTO examiner only when those findings are "contradicted" by new evidence not before the agency. *Kappos v. Hyatt*, 132 S. Ct. 1690, 1696 (2012). Had the Minnesota court applied the correct standard to the record developed on obviousness, it would have concluded that the Michigan court impermissibly overrode a factual determination that was duly committed to and correctly decided by the Ex-

aminer. Once again, the Minnesota court erred in granting judgment on the pleadings.

The Supreme Court has cautioned against "unfairly depriv[ing] the patentee itself of the appellate review that is a component of the one full and fair opportunity to have the validity issue adjudicated correctly." *Cardinal Chem. Co. v. Morton Int'l, Inc.*, 508 U.S. 83, 102 (1993). In its *Caraco* briefing, Novo has demonstrated that the Michigan court's judgment of invalidity was legally erroneous and should be reversed. The same result should follow in *Paddock*.

B. Intervening Decisions Make Clear That The Michigan Court Applied The Wrong Law On Inequitable Conduct

Although Novo explained below that *Therasense* articulated "new legal standards" for inequitable conduct (*see* A2135), the Minnesota court entered judgment on the pleadings because, in its view, the Michigan court's conclusions on inequitable conduct "appear to comport" with *Therasense* (A17). The inequitable conduct issue—which Paddock had not even pleaded as a defense until the Minnesota court granted judgment on the pleadings (A8-A9)—was never subject to discovery in the Minnesota action. The Minnesota court never examined the record on inequitable conduct developed in the *Caraco* litigation, and did not even order briefing or argument on the question of inequitable conduct in light of *Therasense*. Indeed, the parties' only opportunity to address inequitable conduct in light of *Therasense* was through letters filed after briefing on Paddock's motion for judgment

on the pleadings has concluded. *See* A14 n.6. The Michigan court's application of a standard for inequitable conduct later abrogated by *Therasense*, and the Minnesota court's erroneous application of collateral estoppel despite that intervening change in law, cannot stand.

1. *Therasense* Raised The Standard For Inequitable Conduct

In *Therasense*, this Court granted rehearing en banc to address "the problems created by the expansion and overuse of the inequitable conduct doctrine." *Therasense*, 649 F.3d 1285. The en banc Court "tighten[ed] the standards for finding both intent and materiality" (*id.* at 1290) in several important respects:

- To prove inequitable conduct, a challenger must now show by "clear and convincing evidence" that the patentee acted with "specific intent to deceive the PTO." *Therasense*, 649 F.3d at 1290. The en banc Court expressly rejected prior standards based on what the applicant "should have known" or what a "reasonable examiner" could have considered important. *Id.* at 1290, 1294-95.
- In addition, the challenger's clear and convincing evidence of deceptive intent to deceive must be *independent* of the evidence needed to establish materiality. "A district court should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a

strong showing of materiality, and vice versa." *Therasense*, 649 F.3d at 1290.

- A court may infer deceptive intent from circumstantial evidence only when *no* other reasonable inference may be drawn from the evidence. *Therasense*, 649 F.3d at 1290-91.
- The "'patentee need not offer any good faith explanation unless the accused infringer first ... prove[s] a threshold level of intent to deceive by clear and convincing evidence.'" *Therasense*, 649 F.3d at 1291 (alteration in original) (quoting *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1368 (Fed. Cir. 2008)).
- To establish materiality, an accused infringer must now prove that PTO "would not have allowed a claim had it been aware of the undisclosed prior art." *Therasense*, 649 F.3d at 1291. The en banc Court expressly noted that this "but-for" standard differed from past efforts by the Court to address the proliferation of inequitable conduct charges. *Id.*
- The Court expressly rejected a standard for materiality based on PTO Rule 56 found in prior decisions of this Court. *Therasense*, 649 F.3d at 1293-94.

In short, as this Court has recently affirmed, "*Therasense* changed the standard for proving inequitable conduct based on nondisclosure of a reference to the PTO." *1st Media, LLC v. Elec. Arts, Inc.*, 2012 WL 4017301, at *4 (Fed. Cir. Sept. 13, 2012). Many other courts have concluded likewise. *See, e.g., Golden Hour Data Sys., Inc. v. emsCharts, Inc.*, 2012 WL 3494366, at *1 (E.D. Tex. Aug. 15, 2012) ("*Therasense* created a standard contrary to the law previously applied in this case"); *Ohio Willow Wood Co. v. ALPS S., LLC*, 2012 WL 3283437, at *16 (S.D. Ohio Aug. 10, 2012) (referring to the "the heightened standard set forth by the Federal Circuit in *Therasense*"); *Taro Pharms. N. Am. Inc. v. Suven Life Scis., Ltd.*, 2012 WL 2513523, at *5 (D.N.J. June 28, 2012) ("*Therasense* established a more stringent standard for proving inequitable conduct"); *Birchwood Labs., Inc. v. Battenfeld Techs., Inc.*, 2012 WL 2045757, at *9 (D. Minn. May 21, 2012) (*Therasense* "clarified and raised the standards for proving inequitable conduct"); *Bayer Schering Pharma AG v. Watson Pharms., Inc.*, 2012 WL 1079574, at *6 (D. Nev. Mar. 30, 2012) (evidence did not satisfy "*Therasense*'s new inequitable conduct standard"); *Triangle Software, LLC v. Garmin Int'l, Inc.*, 2012 WL 527223, at *3 (E.D. Va. Feb. 14, 2012) ("the *Therasense* decision also imposes significantly more stringent standards for parties seeking to demonstrate inequitable conduct"); *Liquidnet Holdings, Inc. v. Pulse Trading, Inc.*, 2011 WL 2493526, at *1 (S.D.N.Y. June 22, 2011) (*Therasense* "raised the standard of proof required for

inequitable conduct claims"), *aff'd*, 2012 WL 2989246 (Fed. Cir. July 23, 2012); *Ameranth, Inc. v. Menusoft Sys. Corp.*, 2011 WL 2080248, at *1 (E.D. Tex. May 26, 2011) ("The Federal Circuit has recently 'tightened' the standard for finding both intent and materiality" (citing *Therasense*)).

2. The Michigan Judgment Does Not Comport With *Therasense*

The Michigan court, ruling in January 2011, applied standards for inequitable conduct later rejected in *Therasense*. The Minnesota Court subsequently extended that error by giving the Michigan judgment collateral estoppel effect. Both judgments should be reversed. *See 1st Media*, 2012 WL 4017301, at *9 (when a complete record fails to satisfy the heightened standards set forth in *Therasense*, "this court reverses").

As explained in greater detail in Novo's principal brief in the *Caraco* appeal, the Michigan court repeatedly misapplied the standard for inequitable conduct. Among its numerous errors:

- The Michigan court expressly relied on the "should have known" and "reasonable examiner" standards for inferring deceptive intent that this Court rejected in *Therasense*, 649 F.3d at 1290, 1294-95. *E.g.*, A926 (Michigan court stating that an inference of deceptive intent is appropriate when applicant "'knew of the information [and] ... knew or should have known of the materiality of the information'") (altera-

tions in original) (quoting *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1313 (Fed. Cir. 2008)).

- The Michigan court expressly relied on a sliding scale for materiality and intent that this Court rejected in *Therasense*, 649 F.3d at 1290. *E.g.*, A926 (Michigan court stating that "'[t]o the extent that one standard requires a higher showing of materiality than another standard, the requisite finding of intent may be lower'") (quoting *Digital Control v. Charles Mach. Works*, 437 F.3d 1309, 1316 (Fed. Cir. 2006)).
- The Michigan court inferred deceptive intent over more plausible inferences, contrary to *Therasense*, 649 F.3d at 1290-91. *E.g.*, A946 (Michigan court failing to consider more plausible inferences after erroneously shifting the burden of proof to Novo).
- The Michigan court required Novo to prove its good faith, contrary to *Therasense*, 649 F.3d at 1291. *E.g.*, A946 (requiring Novo to prove good faith and drawing a negative inference from *Novo* not calling a witness to testify at trial).
- The Michigan court expressly relied on a standard for materiality based on PTO Rule 56 that this Court rejected in *Therasense*, 649 F.3d at 1293-94. *E.g.*, A944-A945.

In the teeth of these errors, the Minnesota court erred in concluding that the Michigan court's conclusions "appear to comport" with *Therasense*. A17. "As an equitable doctrine, inequitable conduct hinges on basic fairness." *Therasense*, 649 F.3d at 1292. So, too, the equitable doctrine of collateral estoppel, the application of which must "necessarily rest on the trial courts' sense of justice and equity." *Blonder-Tongue*, 402 U.S. at 334. Here, the Minnesota court failed in this basic obligation: At no time did that court examine the record on inequitable conduct developed in the Michigan court or consider whether the facts amounted to clear and convincing evidence of inequitable conduct. *Cf. Therasense*, 649 F.3d at 1290-91. Given the numerous errors of the Michigan court requiring reversal, the Minnesota court's judgment should be reversed as well.

CONCLUSION

The judgment of the district court should be reversed.

Respectfully submitted this 24th day of September, 2012.

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ADDENDA

AO450 (Rev. 5/85) Judgment in a Civil Case

UNITED STATES DISTRICT COURT
District of Minnesota

Novo Nordisk, Inc. and Novo Nordisk A/S

V.

Paddock Laboratories, Inc.

JUDGMENT IN A CIVIL CASE

Case Number: 10-cv-2199 (DWF/JJK)

☐ **Jury Verdict.** This action came before the Court for a trial by jury. The issues have been tried and the jury has rendered its verdict.

☒ **Decision by Court.** This action came to trial or hearing before the Court. The issues have been tried or heard and a decision has been rendered.

IT IS ORDERED AND ADJUDGED THAT:

1. All remaining claims and counterclaims in this action are DISMISSED WITHOUT PREJUDICE pursuant to Federal Rule of Civil Procedure 41(a)(1).

2. Novo Nordisk's motions to dismiss Paddock's antitrust counterclaims (Doc. Nos. [67], [70]), and Paddock's motion for certification of the Court's June 22, 2011 order as a final judgment under Federal Rule of Civil Procedure 54(b) (Doc. No. [117]), are hereby deemed withdrawn without prejudice and the September 1, 2011 hearing is hereby cancelled.

3. Each party in the action shall bear its own costs, expenses, and attorney fees, and waives any right to pursue against any other party an award of costs, expenses, or attorney fees.

4. In order to give full force and effect to the Court's Memorandum and Opinion of November 30, 2010 (Doc. No. [51]) in light of the mutual dismissals set forth above, any future action or claim that the parties decide to pursue against one another arising out of the facts or circumstances alleged in Novo Nordisk's Complaint or Paddock's First Amended Answer and Counterclaim shall be filed in this District. This Court shall retain jurisdiction over this stipulation and any future claim(s) as set forth in this paragraph.

5. Whereas after entry of this Order, there are no remaining claims to be adjudicated, the clerk is directed to enter final judgment in accordance with this Court's June 22, 2011 order (Doc. No. [115]).

6. If a court of appeals vacates or reverses in part or in whole the January 19, 2011 judgment in Novo Nordisk A/S, et al. v. Caraco Pharm. Labs., Ltd., et al., Civil Action No. 2:05 CV 40188 (E.D. Mich.), this Court will, in accordance with Fed. R. Civ. P. 60(b)(5), vacate those corresponding portions of the final judgment and the June 22, 2011 order in this action.

August 30, 2011
Date

RICHARD D. SLETTEN, CLERK

s/L. Brennan
(By) L. Brennan, Deputy Clerk

UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

Novo Nordisk, Inc., and
Novo Nordisk A/S,

Plaintiffs,

v.

Paddock Laboratories, Inc.,

Defendant.

Civil No. 10-2199 (DWF/JJK)

MEMORANDUM OPINION AND ORDER

Aric H. Wu, Esq., Ashley E. Johnson, Esq., Austin V. Schwing, Esq., George A. Nicoud, III, Esq., Josh A. Krevitt, Esq., Michael A. Sitzman, Esq., Wayne M. Barsky, Esq., and M. Sean Royall, Esq., Gibson, Dunn, Crutcher LLP; Chad Drown, Esq., Christopher J. Burrell, Esq., Kenneth A. Liebman, Esq., Faegre & Benson LLP; and W. Todd Miller, Esq., Baker & Miller PLLC, counsel for Plaintiffs.

Rachel K. Zimmerman, Esq., Merchant & Gould PC; and Daniel G. Brown, Esq., Gina R. Gencarelli, Esq., Nicole W. Stafford, Esq., Seth C. Silber, Esq., and Tonia Ouellette Klausner, Esq., Wilson, Sonsini, Goodrich & Rosati PC, counsel for Defendant.

INTRODUCTION

This matter is before the Court on a Motion to Stay Litigation of Patent Claims and Defenses Pending Appeal brought by Plaintiffs Novo Nordisk Inc. and Novo Nordisk A/S (together, "Novo Nordisk") and a Motion for Judgment on the Pleadings Based on Collateral Estoppel and/or Summary Judgment of No Infringement brought by Defendant Paddock Laboratories, Inc. ("Paddock"). For the reasons set forth below, the Court grants in part and denies in part Paddock's motion and denies Novo Nordisk's motion.

BACKGROUND

Novo Nordisk holds United States Patent No. 6,677,358 (the "'358 Patent"), which is directed to and claims a pharmaceutical composition that includes repaglinide in combination with metformin.[1] (Compl. ¶¶ 11, 12 & Ex. A.) Novo Nordisk also holds the FDA-approved New Drug Application ("NDA") for repaglinide, and it manufactures and sells repaglinide under the brand name PRANDIN®. (Compl. ¶ 13.)

In 2005, Caraco Pharmaceutical Laboratories, Ltd., ("Caraco") submitted an Abbreviated New Drug Application ("ANDA") to the FDA seeking approval to engage in the commercial manufacture and sale of a generic form of repaglinide tablets prior to the expiration of the '358 Patent. On June 9, 2005, Novo Nordisk sued Caraco for infringement of the '358 Patent in the United States District Court for the Eastern District of Michigan (the "Michigan court"). (Decl. of Daniel G. Brown ("Brown Decl.") ¶ 5, Ex. 1 (*Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, No. 05-40188 (E.D. Mich. 2005) (the "Michigan Action")).)

In May 2010, Novo Nordisk filed this action alleging infringement of the '358 Patent and seeking a declaration that Novo Nordisk has not violated the Antitrust Laws of the United States, 15 U.S.C. § 1, *et seq.* (Compl. ¶¶ 1, 45, 50.) Novo Nordisk's patent infringement claims are based on Paddock's submission of its ANDA to the FDA seeking approval to engage in the commercial manufacture and sale of a generic form of

[1] Combination therapy with repaglinide and metformin is a treatment for Type 2 diabetes. (Compl. ¶ 10.)

repaglinide. (Compl. ¶¶ 31, 45.) Paddock filed an answer, several affirmative defenses (including the defenses of invalidity due to obviousness and unenforceability due to patent misuse), and six counterclaims (including claims for declarations that the '358 Patent is invalid under the doctrine of obviousness and unenforceable for patent misuse, as well as counterclaims for non-infringement and monopolization).

In June and August 2010, the district court in the Michigan Action held trial on Caraco's counterclaims for invalidity and unenforceability of the '358 Patent. On January 19, 2011, the Michigan court issued a decision ruling: (1) that the '358 Patent is not invalid because of anticipation; (2) that the '358 Patent is invalid because of obviousness; and (3) that the '358 Patent is unenforceable because of inequitable conduct. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, __ F. Supp. 2d __, No. 05-40188, 2011 WL 163996, at *39 (E.D. Mich. Jan. 19, 2011) (the "Michigan Decision"). Judgment was entered and Novo Nordisk appealed from the judgment to the Federal Circuit Court of Appeals. (Decl. of Michael A. Sitzman ("Sitzman Decl.") ¶ 3, Ex. B.)

Presently before the Court are: (1) Novo Nordisk's motion to stay litigation of all patent claims and defenses in this action pending the Federal Circuit's resolution of Novo Nordisk's appeal in the Michigan Action; and (2) Paddock's motion for judgment on the pleadings on Novo Nordisk's patent infringement claim under principles of collateral estoppel.

DISCUSSION

I. Motion to Amend

Paddock seeks, as a preliminary matter, leave to amend its Answer to assert the defenses of collateral estoppel and unenforceability of the '358 Patent due to inequitable conduct.[2] Paddock bases its request on facts revealed in the Michigan Decision. Paddock asserts that the amendment would eliminate any question as to whether collateral estoppel applied to preclude Novo Nordisk's pursuit of its patent claim in this action. Paddock further asserts that good cause has been shown and that there is no undue delay, bad faith, or dilatory motive on its part. Novo Nordisk does not offer arguments opposing Paddock's request to amend its Answer.

There is no dispute that the deadline to amend pleadings in this case has passed. Therefore, the "good cause" standard of Rule 16(b) applies to Paddock's request for leave to amend. *See Freeman v. Busch,* 349 F.3d 582, 589 (8th Cir. 2003); *Birchwood Labs., Inc. v. Battenfeld Techs., Inc.*, 762 F. Supp. 2d 1152, 1154 (D. Minn. 2011). This case is in an early stage of litigation. At the time Paddock filed its motion, neither party had produced documents and no depositions had been noticed or taken. (Brown Decl. ¶¶ 15-23.) Paddock represents that the facts underlying the inequitable conduct defense were unknown prior to the Michigan Decision. Moreover, the record does not suggest

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[2] Paddock attaches its proposed Second Amended Answer and Counterclaims to the the Brown Declaration. (Brown Decl. ¶ 14, Ex. 10.)

any undue delay or bad faith on the part of Paddock. Therefore, the Court concludes that good cause exists and grants Paddock's request to amend its Answer.

II. Motion for Judgment on the Pleadings

A party may move for judgment on the pleadings at any point after the close of pleadings but early enough to avoid a delay of trial. Fed. R. Civ. P. 12(c). A court evaluates a motion for judgment on the pleadings under the same standard as a motion brought under Rule 12(b)(6). *See Ashley County v. Pfizer*, 552 F.3d 659, 665 (8th Cir. 2009); *Westcott v. City of Omaha*, 901 F.2d 1486, 1488 (8th Cir. 1990).

In deciding a motion to dismiss under Rule 12(b)(6), a court assumes all facts in the complaint to be true and construes all reasonable inferences from those facts in the light most favorable to the complainant. *Morton v. Becker*, 793 F.2d 185, 187 (8th Cir. 1986). In doing so, however, a court need not accept as true wholly conclusory allegations, *Hanten v. School District of Riverview Gardens*, 183 F.3d 799, 805 (8th Cir. 1999), or legal conclusions drawn by the pleader from the facts alleged. *Westcott*, 901 F.2d at 1488. A court may consider the complaint, matters of public record, orders, materials embraced by the complaint, and exhibits attached to the complaint in deciding a motion to dismiss under Rule 12(b)(6) of the Federal Rules of Civil Procedure. *Porous Media Corp. v. Pall Corp.*, 186 F.3d 1077, 1079 (8th Cir. 1999).

To survive a motion to dismiss under Rule 12(b)(6), a complaint must contain "enough facts to state a claim to relief that is plausible on its face." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007). Although a complaint need not contain "detailed factual allegations," it must contain facts with enough specificity "to raise a right to relief

above the speculative level." *Id.* at 555. As the United States Supreme Court recently reiterated, the "threadbare recitals of the elements of a cause of action, supported by mere conclusory statements," will not pass muster under *Twombly*. *Ashcroft v. Iqbal*, 129 S. Ct. 1937, 1949 (2009) (citing *Twombly*, 550 U.S. at 555). In sum, this standard "calls for enough fact[s] to raise a reasonable expectation that discovery will reveal evidence of [the claim]." *Twombly*, 550 U.S. at 556. The issue of whether collateral estoppel applies is properly resolved on a motion for judgment on the pleadings. *Blonder-Tongue Labs., Inc. v. Univ. of Illinois Found.*, 402 U.S. 313, 348 (1971).

Paddock asserts that under principles of collateral estoppel it is entitled to judgment on the pleadings on Novo Nordisk's patent infringement claim. Paddock argues that it is entitled to the full enforcement of the Michigan court's determinations that the '358 Patent is unenforceable due to Novo Nordisk's inequitable conduct and that claim 4 of the '358 Patent is invalid for obviousness.

Novo Nordisk opposes Paddock's motion for judgment on the pleadings and asserts that the prudent course would be for the Court to exercise its discretion and stay this action pending appeal.[3] Novo Nordisk contends a stay is warranted here because

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[3] The Court has the inherent power to stay an action to control its docket, conserve judicial resources, and provide a just determination of the case. *See Lunde v. Helms,* 898 F.2d 1343, 1345 (8th Cir. 1990) (*citing Landis v. N. Am. Co.*, 299 U.S. 248, 254-55 (1936)). In determining whether to issue a stay, the Court considers (1) whether a stay would unduly prejudice or present a clear tactical disadvantage to the non-moving party; (2) whether a stay will simplify the issues; and (3) whether discovery is complete and whether a trial date has been set. *VData, LLC v. AETNA, Inc.*, Civ. No. 06-1701, 2006 WL 3392889, at *5 (D. Minn. Nov. 21, 2006).

there is uncertainty regarding the validity of the Michigan Decision and questions regarding the court's jurisdiction in the Michigan Action.

The determinations of patent invalidity and unenforceability are both entitled to collateral estoppel effect in suits by the patentee against other defendants. *Blonder-Tongue*, 402 U.S. at 349-50. *See also Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1382 (Fed. Cir. 1999) (affirming the application of collateral estoppel based on the judgment of invalidity and unenforceability).[4] Under the doctrine of collateral estoppel, Novo Nordisk cannot relitigate the merits of the holdings in the Michigan Decision in this Court if the following requirements are met:

> (1) the party sought to be precluded in the second suit must have been a party, or in privity with a party, to the original lawsuit; (2) the issue sought to be precluded must be the same as the issue involved in the prior action; (3) the issue sought to be precluded must have been actually litigated in the prior action; (4) the issue sought to be precluded must have been determined by a valid and final judgment; and (5) the determination in the prior action must have been essential to the prior judgment.

Robinette v. Jones, 476 F.3d 585, 589 (8th Cir. 2007) (quotation omitted).

There is no dispute that Novo Nordisk was a party in the Michigan Action and that the court in the Michigan Action entered a judgment of invalidity and unenforceability of the '358 Patent. Specifically the court in the Michigan Action held that the '358 Patent is unenforceable because of inequitable conduct in its prosecution and that claim 4 of the

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[4] The Federal Circuit Court of Appeals has explained that "[i]n *Blonder-Tongue* . . . the Supreme Court ruled that once the claims of a patent are held invalid in a suit involving one alleged infringer, an unrelated party who is sued for infringement of those claims may reap the benefit of the invalidity decision under principles of collateral estoppel." *Mendenhall v. Barber-Greene Co.*, 26 F.3d 1573, 1577 (Fed. Cir. 1994).

'358 Patent is invalid for obviousness over the prior art. The issues regarding the invalidity and unenforceability of the '358 Patent are the same issues that are presented in this action. Both Paddock here and Caraco in the Michigan Action have asserted the defenses of obviousness and that the '358 Patent is unenforceable due to Novo Nordisk's inequitable conduct. Further, there is no dispute that the issues regarding the invalidity and unenforceability of the '358 Patent in the Michigan Action were actually litigated. Judgment in the Michigan Action was entered after an 11-day trial and the parties' post-trial briefing on those issues. Finally, the issues regarding the invalidity and unenforceability of the '358 Patent were essential to the judgment in the Michigan Action. The Michigan court's determination of inequitable conduct was the sole basis for the determination that the '358 Patent is unenforceable, and the determination of obviousness was the sole basis for the determination of invalidity. Based on the above, the Court concludes that the requirements for collateral estoppel have been met.[5]

Without disputing that the requirements for collateral estoppel have been met, Novo Nordisk asserts that the case should be stayed pending its appeal of the judgment in the Michigan Action to the Federal Circuit. It is well-settled, however, that for purposes

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[5] Under *Blonder-Tongue*, a prior judgment will not have a collateral estoppel effect if a patentee can demonstrate that it did not have a full and fair opportunity to litigate. 402 U.S. at 332-34. In determining whether a patentee has had a full and fair opportunity to litigate an issue in a prior case, the Court considers factors such as choice of forum, incentive to litigate, whether the court employed the correct legal standard, whether the trier of fact "wholly failed to grasp the technical subject matter and issues in suit," and whether the patentee, without its fault, was deprived of crucial evidence in the first suit. *Blonder-Tongue*, 402 U.S. at 333. Based on the record before it, the Court concludes that none of these factors support re-litigating the issues of validity and unenforceability.

of collateral estoppel, finality attaches at the time of entry of judgment and a pending appeal does not bar the preclusive effect of the judgment. *See, e.g., In re Ewing*, 852 F.2d 1057, 1060 (8th Cir. 1988); *Pharmacia*, 170 F.3d at 1381. Despite this, Novo Nordisk contends that the pending appeal in the Michigan Action and the Federal Circuit's decision in *Therasense, Inc. v. Becton, Dickinson and Co.*, __ F.3d __, No. 2008-1511, 2008-1512, 2008-1514, 2008-1505, 2011 WL 2028255 (Fed. Cir. May 25, 2011), justify deferring a decision on collateral estoppel and instead support the issuance of a stay.

First, Novo Nordisk argues that there is substantial uncertainty regarding the validity of the decision in the Michigan Action and whether the court in the Michigan Action had jurisdiction to enter judgment. In support, Novo Nordisk points out that a district court in New Jersey, in a case involving the same patent and ANDA for generic repaglinide, concluded that it lacked jurisdiction to decide the merits of the patent dispute. *Novo Nordisk Inc. v. Mylan Pharms. Inc.*, C.A. No. 09-2445, 2010 WL 1372437, at *7-13 (D.N.J. Mar. 31, 2010). Novo Nordisk argues that the New Jersey decision is inconsistent with the court's exercise of subject matter jurisdiction in the Michigan Action, and therefore that the decision in the Michigan Action should not be given preclusive effect. In the same vein, Novo Nordisk contends that the Supreme Court may be addressing the alleged jurisdictional defect because, in the Michigan Action, Caraco petitioned the Supreme Court for a writ of certiorari on an interlocutory appeal involving the scope of the Hatch-Waxman Act and Novo Nordisk has opposed the

petition on multiple grounds, including the alleged absence of federal jurisdiction. (Decl. of Aric H. Wu ¶¶ 8-10, Exs. D-F.)

The record indicates that Novo Nordisk had the opportunity to litigate the issue of subject matter jurisdiction in the Michigan Action. Indeed, Novo Nordisk made a motion to dismiss its own patent claims for lack of subject matter jurisdiction at trial in the Michigan Action. (Decl. of Gina R. Gencarelli ("Gencarelli Decl.") ¶ 6, Ex. B at 8.) The Michigan court denied the motion to dismiss and held that jurisdiction existed. (*Id.*) Novo Nordisk has not demonstrated that the Michigan court's exercise of jurisdiction was "seriously defective." *See Blonder-Tongue*, 402 U.S. at 333. Therefore, the Court respectfully declines to consider Novo Nordisk's jurisdictional argument.

Second, Novo Nordisk asserts that the Federal Circuit's *en banc* decision in *Therasense*, rejects the standards of both materiality and intent that were applied by the Michigan court with respect to its finding of inequitable conduct.[6] Novo Nordisk asserts that it would therefore be inequitable to give collateral estoppel effect to the judgment in the Michigan Action. Paddock asserts that the *Therasense* court affirmed the existing standard for determining intent and announced a standard for materiality that is lower than the standard applied in the Michigan Action. Thus, Paddock asserts that the

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[6] In its opposition to Paddock's motion for judgment on the pleadings, Novo Nordisk originally noted that an *en banc* decision of the Federal Circuit in *Therasense* was anticipated. On May 25, 2011, the Federal Circuit issued its *en banc* decision. *Therasense*, 2011 WL 2028255 (Fed. Cir. May 25, 2011). The parties filed supplemental letter briefs addressing the *Therasense* decision.

Therasense decision actually supports the entry of immediate judgment on the basis of collateral estoppel.

In *Therasense*, the Federal Circuit revisited the standards for both materiality and intent with respect to the inequitable conduct defense, and explained:

> [T]he standards for intent to deceive and materiality have fluctuated over time. In the past, this court has espoused low standards for meeting the intent requirement, finding it satisfied based on gross negligence or even negligence. This court has also previously adopted a broad view of materiality, using a "reasonable examiner" standard . . . . Further weakening the showing needed to establish inequitable conduct, this court then placed intent and materiality together on a "sliding scale." . . .
>
> This court embraced these reduced standards for intent and materiality to foster full disclosure to the PTO. This new focus on encouraging disclosure has had numerous unforeseen and unintended consequences. . . .
>
> . . .
>
> This court now tightens the standards for finding both intent and materiality in order to redirect a doctrine that has been overused to the detriment of the public.

Therasense, __ F.3d __, 2011 WL 2028255, at *7-9 (citations and quotations omitted).

The Federal Circuit went on to explain the proper standards:

> To prevail on a claim of inequitable conduct, the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO. A finding that the misrepresentation or omission amounts to gross negligence or negligence under a "should have known" standard does not satisfy this intent requirement. In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference. In other words, the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it.
>
> . . .

> Intent and materiality are separate requirements. A district court should not use a "sliding scale," where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa. Moreover, a district court may not infer intent solely from materiality. Instead, a court must weigh the evidence of intent to deceive independent of its analysis of materiality. Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive.
>
> Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence. However, to meet the clear and convincing evidence standard, the specific intent to deceive must be the single most reasonable inference able to be drawn from the evidence. Indeed, the evidence must be sufficient to require a finding of deceitful intent in the light of all the circumstances. Hence, when there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found.
>
> . . .
>
> The absence of a good faith explanation for withholding a material reference does not, by itself, prove intent to deceive.
>
> . . .
>
> This court holds that, as a general matter, the materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art. Hence, in assessing the materiality of a withheld reference, the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference. In making this patentability determination, the court should apply the preponderance of the evidence standard and give claims their broadest reasonable construction.

(*Id.* at *9-10) (citations and internal quotation marks omitted).

The decision in the Michigan Action was issued prior to the recent ruling in *Therasense*. Novo Nordisk argues that the legal standards used in the Michigan Action are contrary to those now applicable under *Therasense*. The Court therefore examines the standards used by the court in the Michigan Action.

In concluding that the '358 Patent is unenforceable due to inequitable conduct, the Michigan court focused on Novo Nordisk's submission of the Sturis Declaration and the accompanying representations of patent attorney Dr. Richard Bork. The Michigan court concluded that both the Sturis Declaration and representations of Dr. Bork were "highly material" to the patentability of Claim 4 under a "clear and convincing standard." *Novo Nordisk A/S v. Caraco*, __ F. Supp. 2d __, 2011 WL 163996, at *33-34 (¶¶ 142, 146). In addition, the Michigan court concluded that the examiner's reliance on both the Sturis Declaration and Dr. Bork's representations warrants the conclusion that the "but for" materiality test was satisfied. (*Id.*) With respect to intent to deceive, the Michigan court found that there was "clear and convincing evidence" justifying the inference that Sturis and Bork had the intent to deceive, and significantly that no reason other than an intent to deceive would be credible. (*Id.* at *35-36 (¶¶ 153-54) (noting an "intent to deceive is the 'single most reasonable inference to be drawn from the evidence'".) Because the court in the Michigan Action found clear and convincing evidence of both "but for" materiality and intent to deceive under the "single most reasonable inference" standard, the Michigan court's conclusions appear to comport with the standards enunciated in *Therasense*. Thus, the Court discerns no reason to consider the judgment in the Michigan Action to be non-final or to decline to give the judgment collateral estoppel effect.

For all of the reasons stated above, the Court concludes that the factors required for the application of collateral estoppel apply to the judgment in the Michigan Action. Accordingly, the Court concludes that Novo Nordisk's patent claims are precluded. In so holding, the Court also finds that the equities favor the entry of judgment as opposed to a

stay of the present action.[7] Thus, the Court also necessarily denies Novo Nordisk's motion to stay. The Court also denies Paddock's motion for summary judgment on Novo Nordisk's patent infringement claims as to claims 1, 2, 3, and 5 of the '358 Patent. Paddock claims that it is entitled to summary judgment on these claims because its accused product only contains one active ingredient, repaglinide. At the time of the briefing on the present motions, no document or deposition discovery had occurred and no claim construction had been performed. The Court concludes that Paddock's motion for summary judgment on these claims, therefore, is premature and denies the motion without prejudice to bring the motion again in the future.

CONCLUSION

Based on the files, records, and proceedings herein, and for the reasons set forth above, **IT IS ORDERED** that:

1. Novo Nordisk's Motion to Stay Litigation of Patent Claims and Defenses Pending Appeal (Doc. No. [76]) is **DENIED**.

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[7] In opposition to Paddock's motion and in support of its motion to stay, Novo Nordisk submits that a stay would not unduly prejudice Paddock, but that a dismissal would cause substantial prejudice to Novo Nordisk. Novo Nordisk highlights that even though it could re-file its lawsuit against Paddock after a dismissal in this action if the judgment in the Michigan Action is ultimately reversed on appeal, it could not reinstate the statutory 30-month stay that is currently in place with the FDA. The Court concludes, on the record before it, that any prejudice to Novo Nordisk is outweighed by the prejudice that Paddock would suffer if its market entry is delayed. In addition, any harm to Novo Nordisk could be remedied by money damages.

2. Paddock's Motion for Judgment on the Pleadings Based on Collateral Estoppel and/or Summary Judgment of No Infringement (Doc. No. [86]) is **GRANTED IN PART** and **DENIED IN PART** as follows:

a. Paddock's request to file its Second Amended Answer and Counterclaim is **GRANTED**.

b. Judgment on the pleadings is entered in favor of Paddock on Novo Nordisk's patent infringement claim based on the collateral estoppel effect of the judgment of unenforceability of the '358 Patent in the Michigan Action.

c. Judgment on the pleadings is entered in favor of Paddock that claim 4 of the '358 Patent is invalid based on the collateral estoppel effect of the judgment of invalidity of claim 4 of the '358 Patent in the Michigan Action.

d. Paddock's motion for summary judgment for non-infringement of claims 1, 2, 3, and 5 of the '358 Patent is **DENIED**.

Dated: June 22, 2011

s/Donovan W. Frank
DONOVAN W. FRANK
United States District Judge

US006677358B1

(12) **United States Patent**
Müller

(10) **Patent No.: US 6,677,358 B1**
(45) **Date of Patent: Jan. 13, 2004**

(54) **NIDDM REGIMEN**

(75) Inventor: **Peter Gjørtz Müller**, Princeton Junction, NJ (US)

(73) Assignee: **Novo Nordisk A/S**, Bagsvaerd (DK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/459,526**

(22) Filed: **Dec. 13, 1999**

Related U.S. Application Data

(63) Continuation of application No. PCT/DK98/00248, filed on Jun. 12, 1998.
(60) Provisional application No. 60/063,368, filed on Oct. 29, 1997.

(30) **Foreign Application Priority Data**

Jun. 13, 1997 (DK) 0694/97

(51) **Int. Cl.**[7] **A61K 31/155**; A61K 31/4453; A61K 31/451

(52) **U.S. Cl.** **514/331**; 514/635

(58) **Field of Search** 514/331, 635, 514/563

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(List continued on next page.)

Primary Examiner—Phyllis G. Spivack
(74) *Attorney, Agent, or Firm*—Reza Green, Esq.; Richard N. Boak, Esq.; Marc A. Began, Esq.

(57) **ABSTRACT**

The present invention discloses a regimen for the treatment of type 2 diabetes, in which the endogenous secretion of insulin is stimulated in connection with meals, by administering a short-acting, oral hypoglycemic agent. Also, the present invention discloses a method of achieving improvement in glycemic control by combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

5 Claims, 4 Drawing Sheets

OTHER PUBLICATIONS

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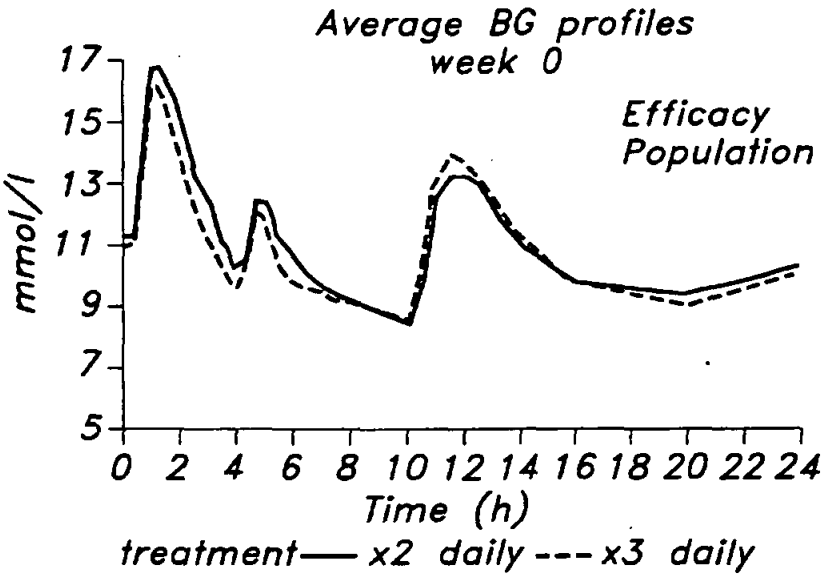

Average BG profiles
week 0
Efficacy
Population
mmol/l
17
15
13
11
9
7
5
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment—— x2 daily --- x3 daily

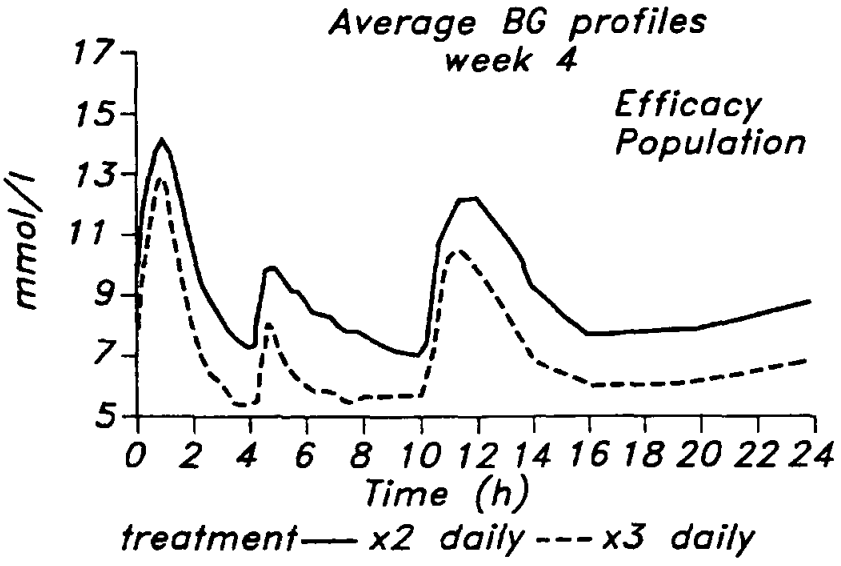

Average BG profiles
week 4
Efficacy
Population
mmol/l
17
15
13
11
9
7
5
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment—— x2 daily --- x3 daily

FIG 1

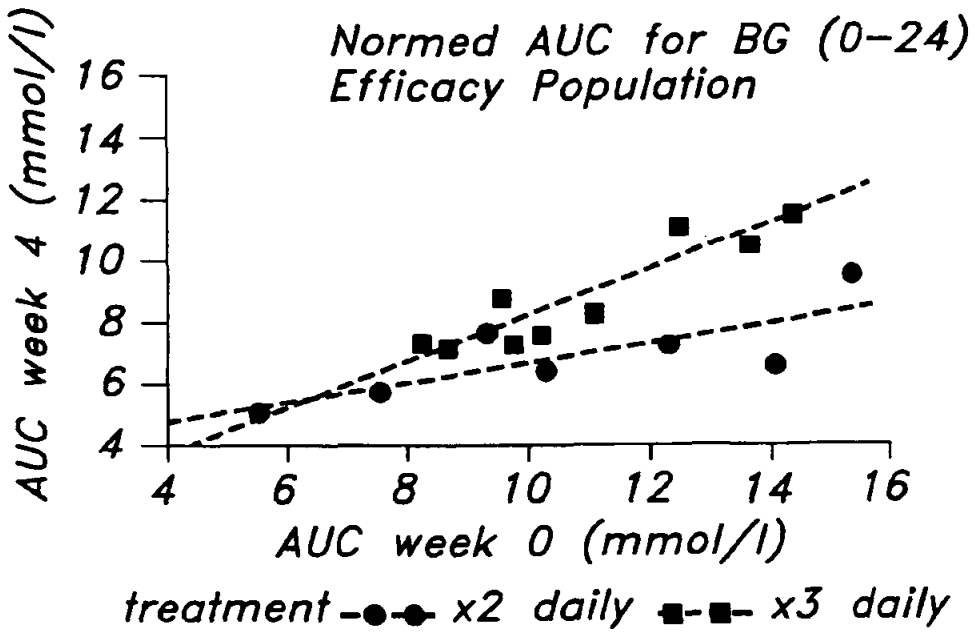
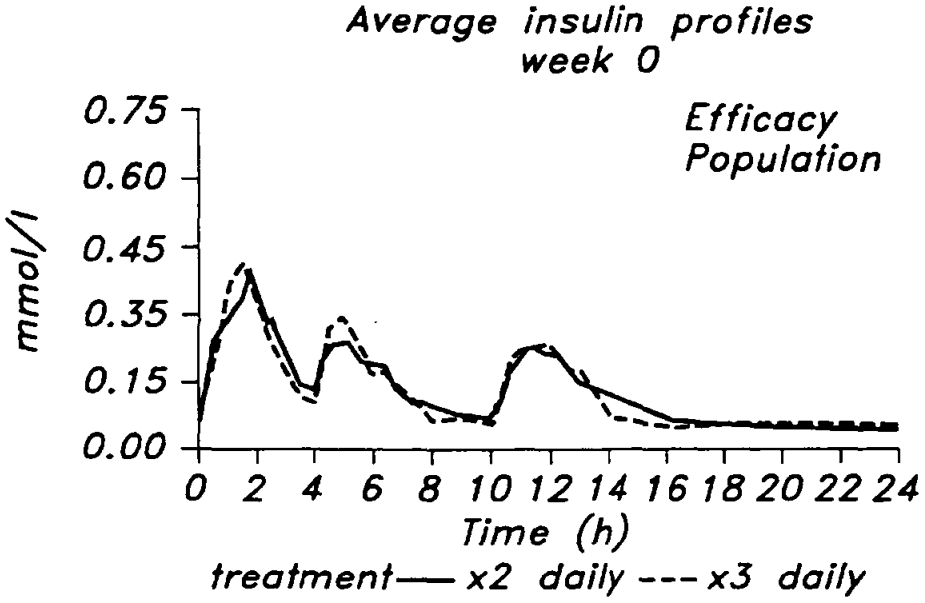

Normed AUC for BG (0–24)
Efficacy Population
AUC week 4 (mmol/l)
16
14
12
10
8
6
4
4
6
8
10
12
14
16
AUC week 0 (mmol/l)
treatment x2 daily x3 daily

FIG 2


Average insulin profiles
week 0
Efficacy
Population
mmol/l
0.75
0.60
0.45
0.35
0.15
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment— x2 daily --- x3 daily

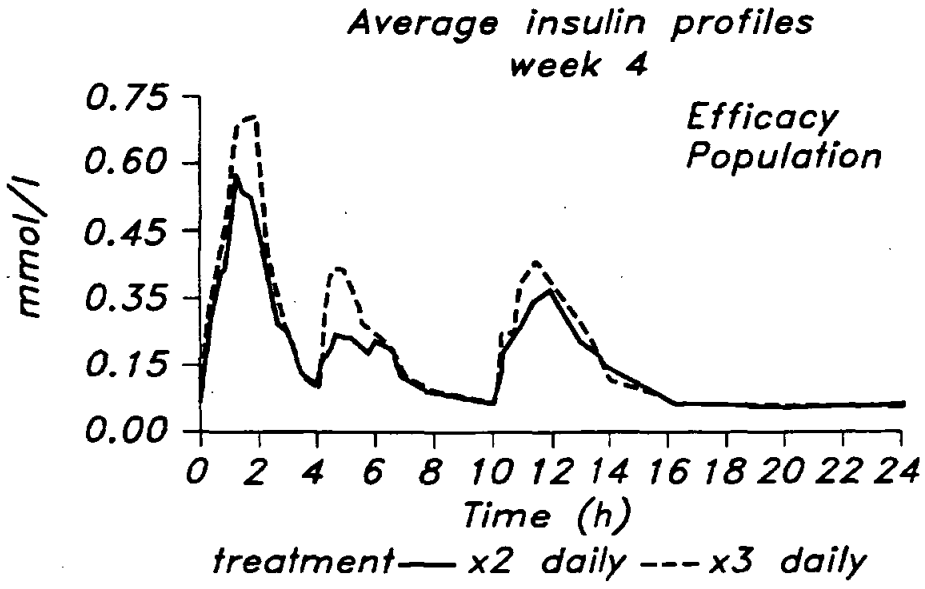

Average insulin profiles
week 4
Efficacy
Population
mmol/l
0.75
0.60
0.45
0.35
0.15
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment— x2 daily --- x3 daily

FIG 3

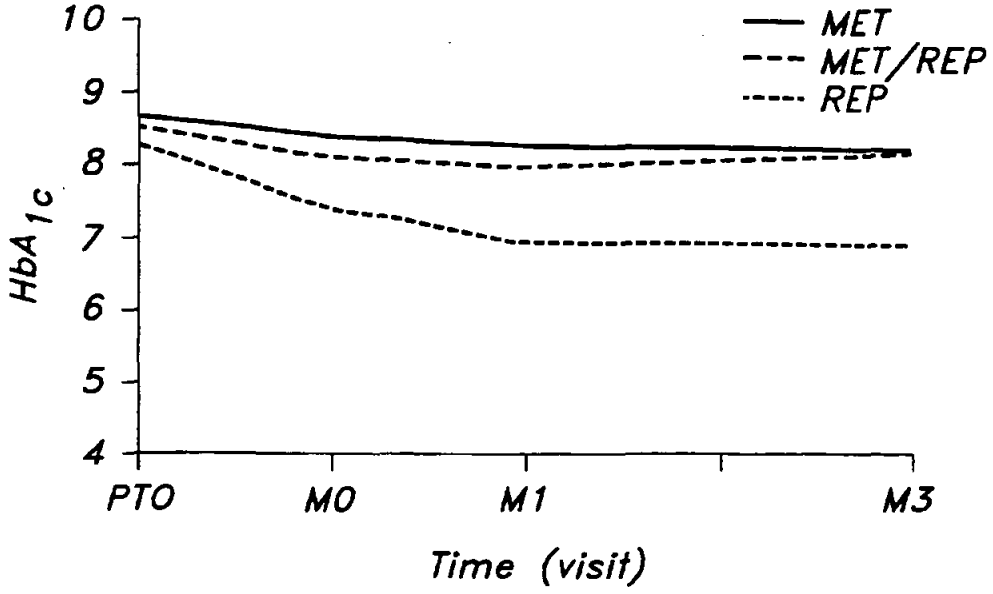

10
9
8
7
6
5
4
HbA1c
MET
MET/REP
REP
PTO
M0
M1
M3
Time (visit)

FIG 4

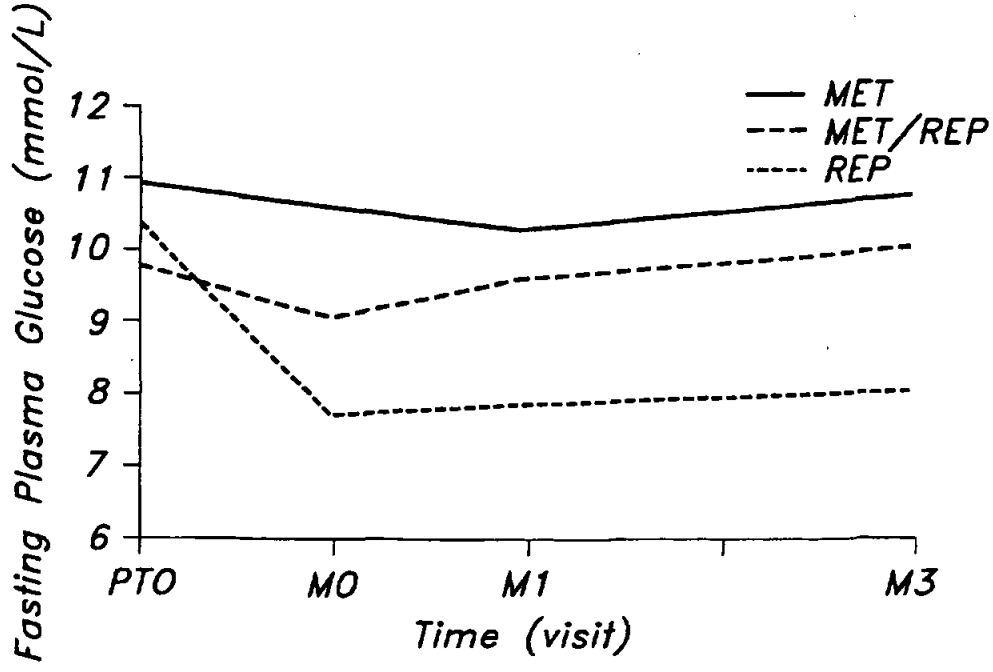

12
11
10
9
8
7
6
Fasting Plasma Glucose (mmol/L)
MET
MET/REP
REP
PTO
M0
M1
M3
Time (visit)

FIG 5

NIDDM REGIMEN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of PCT/DK98/00248 filed on Jun. 12, 1998 and claims priority under 35 U.S.C. 119 of Danish application no. 0694/97 filed on Jun. 13, 1997 and U.S. provisional application No. 60/063,368 filed on Oct. 29, 1997, the contents of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to the use of a short-acting oral hypoglycemic agent and to a novel regimen in the treatment of type 2 diabetes in which the endogenous secretion of insulin is stimulated in connection with meals by administering in connection with the meals a short-acting oral hypoglycaemic agent. Also, the present invention relates to a method of achieving significantly improvement in the glycaemic control by a combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

BACKGROUND OF THE INVENTION

Diabetes is characterised by an impaired glucose metabolism manifesting itself among other things by an elevated blood glucose level in untreated diabetic patients. The underlying defects lead to a classification of diabetes into two major groups: type 1 diabetes, or insulin dependent diabetes mellitus (IDDM), which arises when patients lack β-cells producing insulin in their pancreatic glands, and type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which occurs in patients with an impaired β-cell function besides a range of other abnormalities.

Type 1 diabetic patients are currently treated with insulin, while the majority of type 2 diabetic patients are treated either with agents that stimulate β-cell function or with agents that enhance the tissue sensitivity of the patients towards insulin. Since the agents that stimulate β-cell function or enhance the tissue sensitivity of the patients towards insulin are typically administered orally, these agents are collectively referred to as oral hypoglycemic agents or OHAs.

Among the agents applied for stimulation of the β-cell function, those acting on the ATP-dependent potassium channel of β-cells are most widely used in current therapy. The so-called sulphonylureas such as tolbutamide, glibenclamide, glipizide, and gliclazide are used extensively and other agents such as repaglinide also acting at this molecular site are under development. Repaglinide is (S)-(+)-2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl] butyl]amino]-2-oxo-ethyl]benzoic acid, a compound described i.a. in European patent application publication No. 0 589 874 (to Dr. Karl Thomae GmbH). Among the agents applied to enhance tissue sensitivity towards insulin, metformin is a representative example.

Even though sulphonylureas are widely used in the treatment of NIDDM this therapy is, in most instances, not satisfactory: In a large number of NIDDM patients sulphonylureas do not suffice to normalise blood sugar levels and the patients are, therefore, at high risk for acquiring diabetic complications. Also, many patients gradually lose the ability to respond to treatment with sulphonylureas and are thus gradually forced into insulin treatment. This shift of patients from oral hypoglycaemic agents to insulin therapy is usually ascribed to exhaustion of the β-cells in NIDDM patients.

Over the years, numerous attempts have therefore been made to provide novel agents which stimulate β-cell function in order to offer the NIDDM patients an improved treatment.

SUMMARY OF THE INVENTION

In one preferred aspect, the present invention relates to the use of a short-acting hypoglycemic agent capable of stimulating insulin secretion from β-cells for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM.

In another preferred aspect, the present invention relates to the use of repaglinide for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM.

In another preferred aspect, the present invention relates to the use of A-4166 for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM (A4166 is N-[(trans-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine (Shinkai H et al. J Med Chem 32: 1436–1441)).

In another preferred aspect, the present invention relates to the use of gliquidone for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of a short-acting hypoglycemic agent.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of repaglinide.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of A-4166.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of gliquidone.

In another preferred aspect, the present invention relates to a pharmaceutical kit suitable for use in achieving improved glycaemic control in NIDDM patients, the kit comprising an amount of repaglinide formulated for administration to a NIDDM patient; and a synergistically effective amount of metformin, formulated for administration to the NIDDM patient.

In a further preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of a short-acting hypoglycemic agent supplemented with administration of a long-acting hypoglycemic agent. The long-acting hypoglycemic agent can be administered once per day or divided in sub-doses, preferably two or three sub-doses. Such a regimen may be useful in cases where the patient's basal insulin level is lower than desirable. A preferred short-acting hypoglycemic

agent for use in such a regimen is selected from the group comprising repaglinide, gliquidone and A-4166. A preferred long-acting hypoglycemic agent for use in such a regimen is selected from the group comprising metformin, chlorpropamide, tolbutamide, glibenclamide, glibornuride, gliclazide, glipizide and troglitazone.

Surprisingly, it has been found that when repaglinide is administered together with metformin to NIDDM patients whose glycemic control is poor on metformin alone a significant improvement in the glycaemic control is observed. More particularly, it has been found that there is a synergism between repaglinide and metformin. Thus, in a further preferred aspect, the present invention relates to a method of achieving improved glycemic control in NIDDM patients which comprises administering to a patient in need of such a treatment, an effective amount of repaglinide in a regimen which further comprises treatment with metformin.

In a further preferred aspect, the present invention relates to a pharmaceutical composition which comprises repaglinide and metformin together with a suitable carrier. In one preferred aspect, such a pharmaceutical composition is provided in the form of a tablet. In another preferred aspect, such a pharmaceutical composition is provided in the form of a capsule. Said composition preferably contains from about 0.01 mg to about 8 mg of repaglinide, more preferred from about 0.5 mg to about 6 mg of repaglinide and from about 50 mg to about 1500 mg, preferably from about 100 mg to about 1200 mg of metformin per dose unit.

In the present text, the term "a short-acting hypoglycemic agent" is used to designate a hypoglycemic agent with which maximum secretion of insulin is attained within 1 hour, preferably within 30 min. after administration of the agent, most preferred within 20 min. and which furthermore has a biological half-life, $T_{1/2}$, of less than 2 hours, preferably less than 1.5 hours. The term "a long-acting hypoglycemic agent" is used to designate a hypoglycemic agent with which maximum secretion of insulin is attained more than 1 hour after administration of the agent.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated with reference to the drawings wherein

FIG. 1 shows mean blood glucose profiles at baseline and week 4.

FIG. 2 shows normed AUC for blood glucose (0–24) after 4 weeks versus normed AUC for blood glucose (0–24) at baseline.

FIG. 3 shows mean plasma insulin profiles at baseline and week 4.

FIG. 4 shows changes in HbA_{1c} during the titration (PTO-MO) and maintenance (MO-M3) treatment periods.

FIG. 5 shows changes in fasting plasma glucose during the titration (PTO-MO) and maintenance (MO-M3) treatment periods.

DETAILED DESCRIPTION OF THE INVENTION

Healthy persons have a 24 hour basal secretion of insulin. In connection with meals there is an increased demand for insulin and via a complex feed-back mechanism the pancreas is stimulated to fulfil the demand. After a while, the insulin level again decreases to the basal level.

For the first many years of the disease, dietary restrictions may help NIDDM patients to compensate for the earliest manifestation of their disease which is the decreasing ability of their pancreas to secrete the amount of insulin required in order to control the post prandial blood glucose. At a more progressed state of the disease, also the basal insulin secretion becomes insufficient. When medical treatment becomes necessary, an oral hypoglycemic agent will often be prescribed.

Most of the oral hypoglycemic agents presently in use have a fairly long biological half-life. This implies that when they are administered two or three times per day, which is usually the case, the insulin level will almost constantly be higher than corresponding to the basal level. On the other hand, the peak levels of insulin seen in healthy persons in connection with meals will not be achieved. Such a regimen has certain disadvantages. Thus, it is believed that the diabetic late complications are closely related to a less than optimal glycaemic control caused by, for example, a fairly constantly increased insulin level. Another disadvantage with the long-acting hypoglycemic agents is that they to a very high degree dictate the life-style of the patient: once the patient has taken a long-acting hypoglycemic agent he has only little freedom to deviate from his dietary plan.

The regimen according to the present invention makes it possible for NIDDM patients to mimic the variations in the insulin level seen in healthy persons. Thus, if a patient has a satisfactory basal insulin level, the extra insulin needed in connection with a meal can be secreted by a short stimulation of the pancreas in connection with the meal. Since a short-acting hypoglycemic agent is rapidly absorbed, it can be taken in connection with the meal, preferably shortly before or at the beginning of the meal, optionally during the meal or even shortly after. The resulting stimulation of the pancreas will produce a peak in the insulin level just when it is needed and due to the short half-life of the short-acting hypoglycemic agent, the insulin level will soon go down to the basal level again. The regimen according to the present invention makes it permissible for a NIDDM patient, to a certain degree, to act on an impulse as regards meals and thus adds to the patient's quality of life.

The designation "meal" as used in the present text is intended to mean breakfast, lunch dinner or midnight snack.

When the expression "meal-related" is used in the present text in connection with the administration of a short-acting hypoglycemic agent it preferably designates that the short-acting hypoglycemic agent is administered shortly before or at the beginning of the meal. However, the administration can obviously also take place during the meal or even shortly after without deviating from the idea behind the invention. Thus, the expression "meal-related" preferably means from about 10 minutes before the meal starts to about 10 minutes after the meal is finished, more preferred from about 5 minutes before the meal starts until the meal is finished, most preferred at the beginning of the meal.

If a NIDDM patient does not produce enough insulin to provide a satisfactory basal insulin level, the meal-related administration of a short-acting hypoglycemic agent can be supplemented with the administration of a long-acting hypoglycemic agent. Typically, a long-acting hypoglycemic agent will be administered once, twice or three times per day. Thus, in cases where there is a need to supplement the meal-related administration of a short-acting hypoglycemic agent with a long-acting one, the long-acting one can either be administered at separate hours or together with the short-acting one, optionally in the same tablet or capsule. The advantage of a combined administration is that it is likely to give an improved compliance with the prescribed regimen.

One advantage which can be expected from the regimen according to the present invention is that it, due to its simplicity, will improve the patients' compliance.

Another advantage is that no long-time planning of meals is needed: if the patient has an extra meal he takes an extra tablet, if he skips a meal, he takes no tablet.

A further advantage which can be expected from this regimen is that the patients will have fewer serious diabetic late complications.

Repaglinide is a short-acting hypoglycemic agent with a short half-life. Examples of other short-acting hypoglycemic agents with a short half-lives are gliquidone and A-4166.

Examples of long-acting hypoglycemic agents are biguanides such as metformin and sulphonylureas such as chlorpropamide, tolbutamide, glibenclamide, glibornuride, gliclazide and glipizide. A further example of a long-acting hypoglycaemic agent is troglitazone.

The particular hypoglycemic agent or agents to be used and the optimal dose level for any patient will depend on a variety of factors including the efficacy of the specific agent employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case. It is recommended that the dosage of the hypoglycemic agent or agents of this invention be determined for each individual patient by those skilled in the art.

When repaglinide is given—either alone or in combination with a biguanide or a sulphonylurea or another type of OHA—the amount of repaglinide is preferably in the range of from 0.01 mg to 6 mg, more preferred in the range of from 0.2 mg to 5 mg per meal.

When metformin is given in combination with repaglinide, the daily dosage is preferably in the range of from 200 mg to 3000 mg per day.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention in diverse forms thereof.

EXAMPLES

Example 1

Repaglinide can be Given in a Flexible Dosing Regimen to Patients with Type 2 Diabetes

As evidenced by the present study, the short duration of action ($T_{1/2}$=one hour) makes repaglinide suitable for a meal-related dosing regimen and provides a more flexible everyday life for people with diabetes.

In a single-centre, randomised, open-label, parallel group comparison study it was investigated whether repaglinide given preprandially will maintain glycaemic control in patients who skip a meal (lunch) or have an extra meal (bedtime snack) [mixed regimen] as compared with those who have three regular meals [fixed regimen].

A total of 25 diet-treated patients with type 2 diabetes were enrolled (18 men and 7 women) and given a fixed 1 mg dose of repaglinide preprandially (therapeutic dose range: 0.5–4 mg). After one week of stabilisation patients were randomised to the mixed or fixed regimen for a period of 21 days if blood glucose was >140 mg/dl.

Mean fructosamine values decreased ($p<0.05$) in both groups (fixed: 3.10 to 2.68 mmol/l; mixed: 3.37 to 2.85 mmol/l) with no significant difference between regimen groups. Mean fasting blood glucose (FBG) showed no statistically significant differences between the fixed and mixed groups. Mean FBG decreased to approximately 120 mg/dl in both groups and the difference was not statistically significant. Based on a 37-point blood glucose profile, AUC over 24 hours was not statistically significant between the fixed and mixed groups. When lunch was omitted, blood glucose levels remained stable until next meal. Both dose regimens were well tolerated and no hypoglycaemic episodes or serious adverse events were reported.

Thus, this study demonstrates that patients who occasionally deviate from the recommended meal plan may add an extra meal or skip one, taking repaglinide only when they have a meal, and still maintain their glycaemic control without adverse effect.

Example 2

Improved Glycaemic Control with Repaglinide in NIDDM with 3 Times Daily Meal Related Dosing

Abstract

Repaglinide belongs to a new chemical class of insulin secretagogues and is a short-acting and rapid acting insulin releaser. The potential impact of tailoring insulin release to meal in-take was investigated in a study comparing 3 times daily dosing with repaglinide just before meals to the same dosage administered twice daily. Eighteen OHA-naive NIDDM patients entered a 4-week, single centre, double-blind study, and were randomised to either 0.25 mg repaglinide before breakfast, lunch and dinner (REP3), or 0.5 mg before breakfast, placebo at lunch, and 0.25 mg before dinner (REP2). After two weeks the doses were doubled. At baseline, blood glucose, insulin, and C-peptide profiles were identical between the two groups. After 4 weeks, fasting blood glucose had decreased significantly in both groups (REP2: 11.2 to 9.6 mmol/l and REP3: 11.2 to 8.4 mmol/l). The overall glycaemic control was better in REP3 when compared with REP2, as blood glucose ($AUC_{0-24\ h}$) was 8.91 mmol/l in REP2 and 7.00 mmol/l in REP3 ($P<0.05$). The same significant difference was also found with glucose AUC (0–16 h). This difference in improvement of glycaemic control was reflected in a significant decrease in HbA_{1c} levels in REP3, from 7.5 to 6.5% ($P<0.05$), while HbA_{1c} decreased non-significantly in REP2 (from 7.1 to 6.8%). In both groups plasma insulin decreased to pre-treatment levels before the next meal and there was no increase in plasma insulin during the night time in comparison with pre-treatment levels.

In summary, repaglinide treatment caused significant improvement in glycaemic control in OHA-naive NIDDM patients and administration of the same total daily repaglinide dose showed additional advantages in regard to glycaemic control when given before the three main meals as compared to 2 times daily. At the same time it was possible to avoid both between meals and nocturnal hyperinsulinemia.

Introduction

Repaglinide is a novel insulin secretagogue, which acts on the ATP-sensitive potassium channel in pancreatic β-cells, but binds to a different site from sulphonylureas. Repaglinide has been developed for the treatment of patients with NIDDM whose blood glucose is not adequately controlled by diet alone. Because repaglinide is rapidly absorbed from the gastrointestinal tract and has a short plasma half-life, it is well suited for meal-related administration. The present study was designed to investigate the effects on glycaemic control of repaglinide when given at the same daily dose either morning and evening or preprandially at the three main meals.

Methods

This was a double-blind, placebo-controlled study involving patients with NIDDM, aged 40 to 70 years, with a body mass index >25 kg/m^2, fasting blood glucose (FBG) between 6.5 and 13 mmol/l, HbA_{1c}<11% and fasting C-peptide >0.3 pmol/ml. Of 18 patients enrolled, 17 were randomised to 4 weeks treatment with either 0.25 mg repaglinide three times daily before the three main meals (REP3), or 0.5 mg repaglinide before breakfast, placebo before lunch and 0.25 mg before dinner (REP2). After 2 weeks, the doses were doubled to 0.5 mg before each meal (REP3) and 1 mg+0.5 mg (REP2). Each patient was seen at

three visits during the 4-week study period. A 24-hour hormonal and metabolic profile was examined at baseline and day 28.

Results

Eight patients in the REP3 group and 9 patients in the REP2 group completed the study.

Glycemic Control

After 4 weeks of treatment, blood glucose had decreased in both the REP3 and REP2 groups ($P<0.01$) (FIG. 1). However, preprandial blood glucose values were 1 to 2 mmol/l lower with REP3 than with REP2, and postprandial values were significantly lower, by about 2.5 mmol/l ($P<0.05$).

Mean FBG (±SEM) decreased significantly in both groups ($P<0.001$). In the REP3 group, the decrease was from 11.1±1.24 mmol/l to 8.4±1.01 mmol/l, whilst in the REP2 group, the decrease was from 11.3±0.73 mmol/l to 9.6±0.7 mmol/l. HbA_{1c} (±SEM) also decreased in both groups after 4 weeks of treatment (REP3: 7.51±0.78% vs 6.51±0.64%; REP2: 7.12±0.24% vs 6.84±0.34%), but the decrease was only statistically significant in the REP3 group ($P=0.004$).

When $AUC_{0\text{-}24\ h}$ for glucose after 4 weeks of treatment was plotted versus $AUC_{0\text{-}24\ h}$ for glucose at baseline (FIG. 2), the slope estimates for the REP3 and REP2 groups differed significantly from one another ($P<0.04$). A similar trend towards greater glycaemic control with REP3 than with REP2 was observed for $AUC_{0\text{-}16\ h}$, though the difference between the groups only just reached statistical significance.

Circulating Insulin and C-Peptide

There were no significant differences between the REP3 and REP2 groups in preprandial or postprandial plasma insulin or plasma C-peptide values during the study. Normed $AUC_{0\text{-}24\ h}$ for plasma C-peptide increased in both groups after 4 weeks of treatment. Normed $AUC_{0\text{-}24\ h}$ for plasma insulin increased by 20% in the REP2 group and 35–40% in the REP3 group (FIG. 3), but the difference was not significant. In both treatment groups, plasma insulin decreased to pre-treatment levels before the next meal, and there was no increase in plasma insulin during the night in comparison with pre-treatment levels.

Plasma Repaglinide

The pharmacokinetic profile of repaglinide was characterised by a high peak value in the morning in the REP2 group, and a high peak in the afternoon in the REP3 group. However, the mean $AUC_{0\text{-}9\ h}$ and $AUC_{0\text{-}24\ h}$ for repaglinide were similar in both groups, showing that both groups received matching total daily drug exposure.

Safety Results

No serious adverse events were reported in either treatment group. The only non-serious adverse events were mild hypoglycemic episodes and one case of influenza

Conclusions

Repaglinide produced a significant improvement in glycaemic control in NIDDM patients, with only mild adverse events at the dose levels used. While the two treatment regimens (twice daily and three times daily preprandially) had similar insulin secretion rates, and did not cause 24-hour hyperinsulinemia, the data indicate that greater metabolic control is achieved when repaglinide is dosed prior to the three major meals as compared to before just breakfast and dinner.

Example 3

Additional Treatment with Repaglinide Provides Significant Improvement in Glycemic Control in NIDDM Patients Poorly Controlled on Metformin

Abstract

This multi centre, randomised trial was designed to compare the effect on glycaemic control of repaglinide (REP) in combination with metformin (MET) against monotherapy with either drug in NIDDM patients inadequately controlled on MET alone (mean HbA_{1c}: 8.5%). Eighty three patients were included in this three-armed, double-blind, double-dummy parallel group study. After a 4–5 week run-in period on their usual dose of MET, patients were randomized to either REP or MET monotherapy, or REP+MET combination therapy. The MET dose was kept constant throughout the study (1–3 g/day). The REP dose was determined during a 4–8 week titration phase (initial REP dose: 0.5 mg three times a day before meals; maximum dose: 4 mg three times a day before meals). A 3-month maintenance period followed the titration phase. From the baseline to final visit, combination therapy with MET+REP significantly ($P<0.005$) improved glycemic control compared with REP or MET monotherapy (mean change in HbA_{1c}: −1.41% (MET+REP), −0.38% (REP), −0.33% (MET); mean change in fasting blood glucose (mmol/l): −2.18 (MET+REP), 0.49 (REP), −0.25 (MET). No statistical differences were seen between the two monotherapies and MET+REP combination therapy with respect to fasting insulin and C-peptide levels, and lipid profiles. MET and MET+REP treatment caused more gastrointestinal side effects than REP treatment. No severe hypoglycemic events were observed in any group. In conclusion, REP treatment provided the same glycemic control as MET with less gastrointestinal side effects. REP+MET therapy induced significant improvements in metabolic control in contrast to either REP or MET, bringing HbA_{1c} down into the range of acceptable control. The data also suggest that the combination of REP and MET may have synergistic properties in this type of patient.

Introduction

Repaglinide (REP) is a novel oral hypoglycemic agent which has been developed for the treatment of patients with NIDDM whose blood glucose is not controlled by dietary measures alone. The drug is rapidly absorbed, has a short plasma half-life, binds to a different site from sulfonylureas on the ATP-sensitive potassium channel on pancreatic β-cells, and is excreted via the bile. Repaglinide (REP) stimulates an insulin release profile similar to the physiological postprandial state. As metformin (MET) and REP have complementary mechanisms of action, the aim of the present study was to investigate the efficacy and safety of REP as combination therapy with MET in patients inadequately treated with MET alone.

Methods

This study was a randomised, double-blind, parallel group trial performed at 9 centres in Australia. Eighty-three patients with NIDDM, aged 40–75 years, a body mass index of >21 kg/M^2, and inadequately controlled (HbA_{1c}>7.1%) after more than 6 months of MET treatment were enrolled. After a 4–5 week open baseline period of MET treatment, patients were randomised either to continue on MET at their usual dose (1–3 mg/day) or to treatment with a combination of MET and REP or REP alone. The dose of REP was determined during a 4–8 week titration period (initial dose 0.5 mg three times daily preprandially (three times a day before meals), maximum dose 4.0 mg three times a day before meals). The dose reached at the last titration step was continued during a 3-month maintenance period. The patients were seen at eight scheduled visits.

Results

A total of 83 patients were enrolled in the trial (MET+REP: 27; REP: 29; MET: 27), of whom 74 completed the study (MET+REP: 27; REP: 26; MET: 21).

Glycemic Control and Metabolic Indices

For patients in the MET+REP group, mean HbA_{1c} and fasting plasma glucose (FPG) decreased significantly from 8.32 to 6.91% (p P<0.005) and from 10.22 to 8.04 mmol/l (P<0.005), respectively between baseline and the final visit (FIGS. 4 and 5). There were no significant changes in either parameter for the MET and REP groups (Table 1).

Fasting insulin and C peptide levels increased significantly during the study in the MET+REP and REP groups (P<0.05), but not in the MET group (Table 2).

Patients in the REP group had a small but statistically significant increase in total, HDL- and LDL-cholesterol levels during the study (P<0.05). HDL-cholesterol also increased in the MET group (P<0.05) (Table 3).

Safety Evaluation

A total of 339 adverse events were reported, of which 27 were considered probably or possibly related to study drug.

The frequency of drug-related adverse events was higher in the MET+REP group (59.3%) than in the monotherapy groups (REP: 25.0%; MET: 14.8%). MET+REP and MET treatment caused more gastrointestinal side effects than REP treatment (MET+REP: 14.8%; MET: 7.4%; REP: 3.6%). There were no statistically significant differences between the treatment groups in laboratory tests or vital signs.

Nine patients (33.3%) in the MET+REP group reported hypoglycemic episodes, compared to 3 (17.9%) in the REP group and none in the MET group. None of the hypoglycemic episodes were severe. One third of the patients with hypoglycemic episodes had these in the titration phase. One patient in the MET+REP group recorded 12 of the 30 episodes reported.

During the study, the mean body weight increased in the MET+REP group (+2.4±0.5 kg, P<0.05) and REP group (+2.98±0.49 kg, P<0.05), but decreased in the MET group (−0.86±0.51 kg, NS). The difference between the MET+REP and MET groups was statistically significant (P<0.05).

TABLE 1

Mean change in HbA_{1c} (%) and fasting plasma glucose (FPG) from baseline to the end of the 3-month maintenance eriod.

	Change in HbA_{1c} (%)	95% C.I.	Change in FPG (mmol/l)	95% C.I.
Metformin/ repaglinide	−1.41 ± 0.23	[−1.87; −0.95]*	−2.18 ± 0.45	[−3.07; −1.28]*
Repaglinide	−0.38 ± 0.23	[−0.84; 0.08]	0.49 ± 0.47	[−0.44; 1.42]
Metformin	−0.33 ± 0.24	[−0.80; 0.15]	−0.25 ± 0.47	[−1.18; 0.68]
Metformin/ repaglinide vs repaglinide	−1.03 ± 0.32	[−1.78; −0.29]*	−2.66 ± 0.65	[−4.14; −1.18]*
Metformin/ repaglinide vs metformin	−1.08 ± 0.33	[−1.84; −0.33]*	−1.92 ± 0.65	[−3.40; −0.44]*

Data are means ± SEM. *P < 0.05

TABLE 2

Mean change in fasting insulin and C peptide from baseline to the end of the maintenance treatment period.

Treatment groups	Change in fasting insulin (mU/l)	95% C.I.	Change in C peptide (nmol/l)	95% C.I.
Metformin/ repaglinide	4.23 ± 1.50	[1.24; 7.23]*	0.17 ± 0.07	[0.03; 0.30]*
Repaglinide	4.04 ± 1.56	[0.93; 7.16]*	0.18 ± 0.07	[0.03; 0.30]*
Metformin	1.05 ± 1.60	[−2.13; 4.23]	0.02 ± 0.07	[−0.13; 0.16]
Metformin/ repaglinide vs repaglinide	0.19 ± 2.17	[4.78; 5.15]	−0.01 ± 0.10	[−0.24; 0.21]
Metformin/ repaglinide vs metformin	3.18 ± 2.19	[−1.84; 8.20]	0.15 ± 0.10	[−0.07; 0.38]

Data are means ± SEM. *P < 0.05.

TABLE 3

Changes (mean ± SD) in lipid profiles (mmol/l) between baseline and the end of the maintenance treatment period.

	MET	MET + REP	REP
Total cholesterol	0.13 ± 0.13	0.13 ± 0.12	0.38 ± 0.12*
HDL cholesterol	0.07 ± 0.03*	0.05 ± 0.03	0.09 ± 0.03*
LDL cholesterol	0.10 ± 0.12	0.11 ± 0.11	0.41 ± 0.12
Triglycerides	−0.20 ± 0.17	−0.10 ± 0.16	0.09 ± 0.16

*P < 0.05

Conclusions

Combination therapy with REP and MET provides better glycemic control than either REP or MET monotherapy in NIDDM patients who are inadequately controlled on metformin alone. Indeed, MET+REP treatment reduced HbA_{1c} of this group of patients to the target value recommended by the American Diabetes Association (<7%).

What is claimed is:

1. A pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier.

2. A pharmaceutical composition of claim 1 provided in the form of a tablet.

3. A pharmaceutical composition of claim 1 provided in the form of a capsule.

4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

5. A kit for use in the treatment of a patient having non-insulin dependent diabetes mellitus (NIDDM), said kit comprising an amount of repaglinide formulated for administration to said patient and an amount of metformin formulated for administration to said patient.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that on September 24, 2012, two copies of the forgoing brief were served, as indicated below, via electronic mail and/or next-day delivery by third-party commercial carrier on the following counsel.

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B). This brief contains 6,723 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Fed. Cir. R. 32(b). Microsoft Word 2003 was used to calculate the word count.

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally-spaced typeface using Microsoft Word 2003 in 14-point Times New Roman type style.

Mark A. Perry/lt

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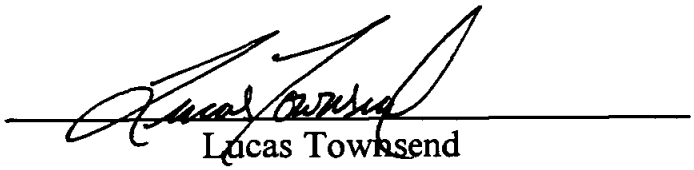
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

Novo Nordisk v. Paddock Labs
No. 2012-1031

CERTIFICATE OF AUTHORITY

I, Lucas Townsend, declare under penalty of perjury that I am authorized by Mark A. Perry, counsel for Novo Nordisk Inc. and Novo Nordisk A/S, to sign on his behalf the attached Principal Brief for Novo Nordisk, Certificate of Interest, Certificate of Service, and Certificate of Compliance.

Executed on September 24, 2012, in Washington, D.C.



Lucas Townsend